=> d l10 ibib abs hitrn 1-38

FILE 'REGISTRY' ENTERED AT 11:21:06 ON 24 MAY 2002
E "CYCLIN-DEPENDENT KINASE INHIBITOR P27"/CN
L1 1 SEA "CYCLIN-DEPENDENT KINASE INHIBITOR P27KIP1 KINASE"/CN
E "CYCLIN DEPENDENT KINASE INHIBITOR P27"/CN
L2 5 SEA ("CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (HUMAN LGH11 KIDNEY)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (HUMAN P27-KIP1)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (MINK MV1LU CELL N-TERMINAL FRAGMENT)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (MOUSE 1EXLOX EMBRYO)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (SUS SCROFA)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1R (SUS SCROFA)"/CN)
L3 6 SEA L1 OR L2

FILE 'HCAPLUS' ENTERED AT 11:24:43 ON 24 MAY 2002
L4 446 SEA L3 OR ((CYCLIN(W)DEPENDENT)(2A)KINASE OR CDK)(5A)(P27 OR P 27)
L5 16 SEA L4 AND (METASTAS? OR METASTAT?)
L6 29 SEA L4 AND (SMC OR (SMOOTH MUSCLE OR TUMOR OR TUMOUR)(W)CELL)
L7 5 SEA L4 AND ((TREAT? OR THERAP?)(5A)(ATHEROSCLER? OR ARTERIOSCLER? OR ARTERIOPATH? OR RESTENOSIS) OR (CARDIOVASCULAR OR CARDIO VASCULAR OR CARDIAC OR HEART)(5A)(DISORDER OR DISEAS?))
~~L8 48 SEA L5 OR L6 OR L7~~
L9 19 SEA L6 AND (MIGRAT? OR PROLIFERAT?)
L10 38 SEA L5 OR L7 OR L9

L10 ANSWER 1 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:902256 HCAPLUS
DOCUMENT NUMBER: 136:322573
TITLE: Mechanisms underlying maintenance of **smooth muscle cell** quiescence in rat aorta: role of the cyclin dependent kinases and their inhibitors
AUTHOR(S): Izzard, Tanya D.; Taylor, Christine; Birkett, Sonia D.; Jackson, Christopher L.; Newby, Andrew C.
CORPORATE SOURCE: Bristol Royal Infirmary, Bristol Heart Institute, Bristol, BS2 8HW, UK
SOURCE: Cardiovascular Research (2002), 53(1), 242-252
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: The authors sought to understand why **smooth muscle cell proliferation** is effectively repressed in intact rat aortic tissue. Methods: Quiescent isolated rat aortic smooth muscle cells and segments of intact rat aorta were stimulated with 10% serum and the time course of expression and activity of proteins involved in cell cycle control were detd. Results: After serum stimulation, smooth muscle cells in intact aortic tissue exhibit no **proliferation**, whereas isolated cells entered S phase 14-16 h later. Activation of ERKs 1 and 2, and induction of cyclin D1 occurred both in isolated cells and aortic tissue. Regulation of Cdk4, cyclin E and Cdk2 protein levels was also not different. Levels of the **cyclin-dependent kinase** inhibitors (CKIs), p16 and **p27**, were initially high in quiescent isolated cells and tissue; levels were downregulated by serum in isolated cells but not in aortic tissue. Cyclin D1/Cdk4, and cyclin E/Cdk2 kinases were active before S phase entry in isolated cells, but remained inactive in aortic

tissue. Conclusions: Cell cycle entry is prevented in aortic tissue, and this is assocd. with an inability to downregulate p16 and p27 CKIs, and therefore to activate cyclin D1 and cyclin E assocd. kinase activities.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:698036 HCAPLUS
DOCUMENT NUMBER: 135:271298
TITLE: cDNA and protein sequence of novel proteasome resistant cyclin dependent kinase inhibitor p27kip1R from pig and their uses in repression of **tumor cell proliferation**
INVENTOR(S): Hirano, Katsuya
PATENT ASSIGNEE(S): Kyushu University, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001258561	A2	20010925	JP 2000-76840	20000317

AB This invention provides a novel novel proteasome resistant cyclin dependent kinase inhibitor p27kip1R from pig. Compared with conventionally identified cyclin dependent kinase inhibitors the p27kip1R differs in C-terminal sequence and lacks Threonine at position 187, the cleavage site of the proteasome, resulting in resistance to the proteasome. The p27kip1R showed resistance to proteasome in in vitro and the expression of p27kip1R in HeLa cells repressed the **proliferation** of the cancel cells. The the stably expression of p27kip1R gene can be used as gene **therapy** for cancer and lesion of **arteriosclerosis.**
IT **351389-76-9 362648-40-6**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(amino acid sequence; cDNA and protein sequence of novel proteasome resistant cyclin dependent kinase inhibitor p27kip1.RHO. from pig and their uses in repression of **tumor cell proliferation**)

L10 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:645086 HCAPLUS
DOCUMENT NUMBER: 136:230126
TITLE: Cell Cycle Aberrations in the Pathogenesis of Squamous Cell Carcinoma of the Uterine Cervix
AUTHOR(S): Clarke, B.; Chetty, R.
CORPORATE SOURCE: Department of Anatomical Pathology, Nelson R. Mandela Medical School, School of Pathology and Laboratory Medicine, Durban, S. Afr.
SOURCE: Gynecologic Oncology (2001), 82(2), 238-246
CODEN: GYNOA3; ISSN: 0090-8258
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cancer cells are characterized by limitless proliferative autonomy and immunity to inhibitory and apoptotic signals, thus ensuring

growth and **metastasis**. Epidemiol. studies have long implicated human papillomavirus (HPV) as a pathogenic agent in cervical cancer. Progress in cancer research now provides an understanding of how these characteristics are achieved by the interaction of HPV proteins with the cell cycle machinery. Expression of oncoproteins E7 and E6 induces immortalization of cells through their inhibitory effects on tumor suppressor proteins pRb and p53, resp. Undermining of pRb's growth-inhibitory role with release of E2F transcription factors renders the cells independent of mitogenic stimuli. The abundance of growth transcription factors grants limitless proliferative potential by allowing expression of products such as cyclins A, E, and B, dihydrofolate reductase, and DNA polymerase which fuel the various stages of the cell cycle. There is subsequent disruption of both the G1-S and G2-M cell cycle checkpoints. Overexpression of cyclin E results in chromosomal instability and possible unmasking of genetic mutations, allowing disease progression. Cyclin A grants anchorage-independent growth, facilitating tissue invasion and tumor spread. Apoptotic and growth-inhibitory mechanisms are also evaded. p53 is degraded by E6 and its own downstream protein mdm2. Its other downstream protein, p21 is rendered ineffective against cyclin-**cyclin-dependent kinase** units by E7, as is **p27**. The understanding of the mol. pathol. of disease will provide us with the ability to prognosticate and treat patients more effectively. (c) 2001 Academic Press.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:561673 HCAPLUS
DOCUMENT NUMBER: 135:270975
TITLE: Connexin43 suppresses **proliferation** of osteosarcoma U2OS cells through post-transcriptional regulation of p27
AUTHOR(S): Zhang, You-Wei; Morita, Ikuo; Ikeda, Masaaki; Ma, Kai-Wen; Murota, Seiitsu
CORPORATE SOURCE: Department of Cellular Physiological Chemistry, Tokyo Medical and Dental University, Tokyo, 113-8549, Japan
SOURCE: Oncogene (2001), 20(31), 4138-4149
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Many lines of evidence indicate that connexin genes expressing gap junction (GJ) proteins inhibit **tumor cell proliferation**. However, the precise mol. mechanisms remain unclear. In this study, we show that overexpression of connexin43 (Cx43) suppressed **proliferation** of human osteosarcoma U2OS cells through inhibition of the cell cycle transition from G1 to S phase. This inhibition was attributed to a significant accumulation of the hypophosphorylated retinoblastoma (Rb) protein, which was causally related to decreases in the kinase activities of cyclin-dependent kinases (CDKs) 2 and 4. Enforced Cx43 expression markedly increased the level of the **CDK** inhibitor **p27**. This increase resulted from an increased synthesis and a reduced degrdn. of the p27 proteins, but not influence of the p27 mRNA. Moreover, we show that the Cx43-modulated GJ function was the main contributor to the elevation in p27 levels, in which cAMP was involved. These data suggest that Cx43 appears to inhibit **proliferation** of U2OS cells by increasing the levels of p27 proteins via post-transcriptional regulatory mechanisms.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:493506 HCAPLUS
DOCUMENT NUMBER: 136:241346
TITLE: Effect of p27 deficiency and rapamycin on intimal hyperplasia: in vivo and in vitro studies using a p27 knockout mouse model
AUTHOR(S): Roque, Merce; Reis, Ernane D.; Cordon-Cardo, Carlos; Taubman, Mark B.; Fallon, John T.; Fuster, Valentin; Badimon, Juan J.
CORPORATE SOURCE: Cardiovascular Biology Research Laboratories, Cardiovascular Institute, Mount Sinai School of Medicine, New York City, NY, 10029-6574, USA
SOURCE: Laboratory Investigation (2001), 81(6), 895-903
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rapamycin, an immunosuppressant and antiproliferative agent, reduces intimal hyperplasia after arterial injury in animal models and in a preliminary study in humans. Rapamycin treatment reportedly increases expression of **p27**, a **cyclin-dependent kinase** inhibitor. This mechanism was tested using a p27-deficient (p27 -/-) murine model. Aortic smooth muscle cells from wild-type (WT) and p27 -/- mice were isolated and cultured. Cell **proliferation**, assessed by cell count and 3H-thymidine incorporation, was inhibited significantly by rapamycin in WT and p27 -/- cells at concns. of 1 ng/mL, 10 ng/mL, and 100 ng/mL ($p < 0.05$, vs. control). The in vivo effect on intimal hyperplasia was studied in p27 -/- and WT mice after femoral artery transluminal injury. Rapamycin treatment was started 2 days before injury and maintained for 2 wk (1 mg/kg per 48 h, i.p.). No significant differences in intima-to-media ratio were found between WT (1.1 .+-. 0.1) and p27 -/- mice (1.0 .+-. 0.1) 4 wk after injury. Rapamycin significantly ($p < 0.05$) reduced intima-to-media ratios in both WT (0.7 .+-. 0.1) and p27 -/- mice (0.5 .+-. 0.1), compared with untreated mice. The p27 deficiency did not alter the arterial wall **proliferative** response to injury. The inhibitory effect of rapamycin on intimal hyperplasia occurred via a p27-independent mechanism. The in vitro data showed that this effect was mediated through decreased **proliferation** and enhanced apoptosis.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:491879 HCAPLUS
DOCUMENT NUMBER: 136:230204
TITLE: Clinicopathological significance of p27 gene expression in cervical carcinomas
AUTHOR(S): Zhang, Keqiang; Su, Qi; Su, Jian; Xu, Jinhua
CORPORATE SOURCE: The Second Affiliated Hospital, Nanhua University, Hengyang, 421001, Peop. Rep. China
SOURCE: Hunan Yixue (2001), 18(2), 90-92
CODEN: HUYIER; ISSN: 1001-9421
PUBLISHER: Hunan Yixue Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The clinicopathol. significance of p27 gene expression in cervical carcinomas was studied. Expression of p27 protein was examd. in paraffin embedded sections of cervical carcinomas by conjugated

streptavidin-peroxidase method. The p27 protein expression was found in 19% and 100% of cervical carcinomas and normal cervical tissues, resp. The p27 protein expression in cervical carcinomas was affected by the tumor differentiation grade and lymph node **metastasis**. Apparently, the p27 gene expression is related to the occurrence, differentiation degree and lymph node **metastasis** of cervical carcinoma. Detection of p27 protein expression may be useful as referential criteria for diagnosis and clin. comprehensive therapy of cervical carcinomas.

L10 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:427691 HCAPLUS
DOCUMENT NUMBER: 136:35501
TITLE: Decreasing of p27Kip1 and cyclin E protein levels is associated with progression from superficial into invasive bladder cancer
AUTHOR(S): Kamai, T.; Takagi, K.; Asami, H.; Ito, Y.; Oshima, H.; Yoshida, K-I.
CORPORATE SOURCE: Department of Urology, Dokkyo University School of Medicine, Tochigi, Japan
SOURCE: British Journal of Cancer (2001), 84(9), 1242-1251
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The p27Kip1 (**p27**) protein is a **cyclin-dependent kinase** inhibitor of the transition from G1 to S phase. It was reported that decreased p27 protein level is a neg. prognostic indicator in human tumors including bladder cancer. We studied the relationship between protein levels of p27, cyclin E and Ki-67 and clinicopathol. features of 145 consecutive Japanese patients with transitional cell carcinoma of the bladder using immunohistochem. staining. Low protein levels of p27 were assocd. with low staining of cyclin E ($P = 0.0302$), high Ki-67 index ($P = 0.0306$), poorly differentiated grade ($P = 0.0006$), muscle invasion ($P = 0.0019$) and lymph node **metastasis** ($P = 0.0002$). Low staining of cyclin E and high Ki-67 index correlated with poorly differentiated grade, muscle invasion and lymph node **metastasis**. Cyclin E protein levels was inversely related with Ki-67 index ($P = 0.0002$). Kaplan-Meier plots of survival rate in patients with low vs. high p27 staining showed that low protein levels of p27 were assocd. with a shortened disease-free and overall survival ($P < 0.0001$ and $P < 0.0001$, resp.). Similarly, low staining of cyclin E and high Ki-67 index correlated with a shortened disease-free and overall survival. On multivariate anal. using Cox proportional hazards model, low protein levels of p27 and high Ki-67 index were independent predictors of shortened disease-free ($P < 0.0001$, $P = 0.0031$, resp.), and low protein levels of p27, low staining of cyclin E and high Ki-67 index of overall survival ($P = 0.0017$, $P = 0.0009$, $P = 0.0003$, resp.). In superficial bladder tumors (Ta, T1; 86 patients), significant correlations were obsd. between low p27 staining and high Ki-67 index and early recurrence ($P = 0.0048$, $P = 0.0178$, resp.). Among the recurrenced superficial tumors (35 patients), the tumors which remained at a low stage showed high protein levels of p27 and cyclin E, and the tumors which progressed to invasive disease showed a gradual decrease in p27 and cyclin E protein levels over time. These findings suggest that decreased protein levels of p27 and cyclin E play a role in the progression of bladder cancer and to evaluate these protein levels may be useful in management of the diseases.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:381964 HCAPLUS
DOCUMENT NUMBER: 135:356011
TITLE: Expression and clinical significance of the G1-S modulators in intrahepatic cholangiocellular carcinoma
AUTHOR(S): Ito, Yasuhiro; Takeda, Tsutomu; Sasaki, Yo; Sakon, Masato; Yamada, Terumasa; Ishiguro, Shingo; Imaoka, Shingi; Tsujimoto, Masahiko; Matsuura, Nariaki
CORPORATE SOURCE: Department of Surgery, Osaka Seamen's Insurance Hospital, School of Allied Health Science, Osaka University Faculty of Medicine, Osaka, 565-0871, Japan
SOURCE: Oncology (2001), 60(3), 242-251
CODEN: ONCOBS; ISSN: 0030-2414
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To elucidate the clin. roles of G1-S modulators in cholangiocellular carcinoma (CCC). We performed immunohistochem. using antibodies against the retinoblastoma gene product (pRb), p16, p21, p27, p53 and cyclin D1 for 41 cases of CCC as well as normal bile ducts. The p27 labeling index (LI) was significantly higher in cases without lymph node **metastasis** than in normal bile ducts, but it decreased greatly in cases with lymph node **metastasis**. It was inversely related to the Ki-67 LI. The p16 LI also showed a relationship with lymph node **metastasis**, but not with the Ki-67 LI. The p21 LI was even higher in poorly differentiated cases and showed a direct relationship with the Ki-67 LI, although it is a neg. regulator of the cell cycle. PRb expression did not correlate with any clinicopathol. features. Cyclin D1 overexpression was more frequently obsd. in cases with poor or moderate differentiation and with lymph node **metastasis**. Cyclin D1 overexpression and aberrant p53 expression showed direct relationships with the Ki-67 LI. These results suggest that in CCC: (1) p27 expression reflects the biol. character of the carcinoma and may regulate its progression; (2) cyclin D1 plays a crucial role in cell cycle progression, and (3) aberrant p53 expression has some effect on CCC cell proliferating activity.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:180633 HCAPLUS
DOCUMENT NUMBER: 134:232250
TITLE: Expression of cell cycle proteins in blood vessels of angiotensin II-infused rats. Role of AT1 receptors
AUTHOR(S): Diep, Quy N.; El Mabrouk, Mohammed; Touyz, Rhian M.; Schiffrin, Ernesto L.
CORPORATE SOURCE: Multidisciplinary Research Group on Hypertension, Clinical Research Institute of Montreal, University of Montreal, Quebec, Can.
SOURCE: Hypertension (2001), 37(2, Pt. 2), 604-609
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Angiotensin II is an important modulator of cell growth through AT1 receptors, as demonstrated both in vivo and in vitro. The authors investigated the role of proteins involved in the cell cycle, including cyclin D1, cyclin-dependent kinase 4 (cdk4), and **cyclin-dependent kinase** inhibitors p21 and **p27** in

blood vessels of angiotensin 1-infused rats and the effect therein of the AT1-receptor antagonist losartan. Male Sprague-Dawley rats were infused for 7 days with angiotensin II (120 ng/kg per min SC) and/or treated with losartan (10 mg/kg per day orally). DNA synthesis in mesenteric arteries was evaluated by radiolabeled 3H-thymidine incorporation. The expression of cyclin D1, cdk4, p21, and p27, which play crit. roles during the G1-phase of the cell cycle process, was examd. by Western blot anal. Tail-cuff systolic blood pressure (mmHg) was elevated (P<0.01, n=9) in angiotensin II-infused rats (161.3.+-.8.2) vs. control rats (110.1.+-.5.3) and normalized by losartan (104.4.+-.3.2). Radiolabeled 3H-thymidine incorporation (cpm/100 .mu.g DNA) showed that angiotensin II infusion significantly increased DNA synthesis (152.+-.5% vs. 102.+-.6% of control rats, P<0.05). Expression of cyclin D1 and cdk4 was significantly increased in the angiotensin II group to 213.7.+-.8% and 263.6.+-.37% of control animals, resp., whereas expression of p21 and p27 was significantly decreased in the angiotensin II group to 23.2.+-.10.4% and 10.3.+-.5.3% of control animals, resp. These effects induced by angiotensin II were normalized in the presence of losartan. Thus, when AT1 receptors are stimulated in vivo, DNA synthesis is enhanced in blood vessels by activation of cyclin D1 and cdk4. Redn. in cell cycle kinase inhibitors p21 and p27 may contribute to activation of growth induced by in vivo AT1 receptor stimulation.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:65870 HCAPLUS
DOCUMENT NUMBER: 134:250442
TITLE: Unusual deregulation of cell cycle components in early and frank estrogen-induced renal neoplasias in the Syrian hamster
AUTHOR(S): Liao, De-Zhong Joshua; Hou, Xiaoying; Bai, Shan; Li, Sara Antonia; Li, Jonathan J.
CORPORATE SOURCE: Hormonal Carcinogenesis Laboratory, Division of Etiology and Prevention of Hormonal Cancers, Kansas Cancer Institute, University of Kansas Medical Center, Kansas, KS, 66160-7412, USA
SOURCE: Carcinogenesis (2000), 21(12), 2167-2173
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is strong evidence that estrogens are involved in the etiol., promotion and progression of a variety of cancers, including the cancers of the breast and endometrium. The Syrian hamster estrogen-induced, estrogen-dependent renal neoplasm is a well-established animal model used to elucidate the cellular and mol. mechanisms involved in solely estrogen-induced carcinogenic processes. G1 cell cycle progression was studied in estrogen-induced early renal tumor foci and in large kidney tumors of castrated male hamsters. Levels of cyclin D1, cyclin E and retinoblastoma (pRb) proteins were higher in these renal neoplasias than in adjacent uninvolved renal tissue and kidneys from untreated, age-matched animals. Of particular interest is the presence of a predominant 35 kDa cyclin E protein variant form in primary renal tumors. In addn., amts. of the phosphorylated forms of cyclin-dependent kinases (cdk) 2 and 4 were decreased, and both RNA and protein levels of p27kip1 (**p27**), a **cyclin-dependent kinase** inhibitor, were markedly higher in early and frank renal tumors than in adjacent uninvolved renal tissue and kidneys of untreated, age-matched animals. These changes in cell cycle components coincided with a rise in

renal **tumor cell proliferation**. Binding of the elevated p27 protein to cyclin E, cdk2 and cdk4, however, was not impaired, suggesting that this cell cycle suppressor protein is functional. In addn., cyclin D1-, cdk2-, cdk4- and cyclin E-assocd. kinase activities were also lower in these estrogen-induced renal neoplasms than in untreated, age-matched kidneys. Interestingly, when compared with untreated kidney tissue, early and frank renal neoplasms had less of the 62 kDa native form of E2F1 and contained a 57 kDa variant form. Thus we have characterized an unusual deregulation of the cell cycle during estrogen-induced renal tumorigenesis in Syrian hamsters which still allows for estrogen-driven kidney **tumor cell proliferation** and may contribute to the early genomic instability found.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:869074 HCAPLUS
DOCUMENT NUMBER: 135:14092
TITLE: Novel chimeric p16 and p27 molecules with increased antiproliferative activity for vascular disease gene therapy
AUTHOR(S): Lamphere, Lou; Tsui, Lisa; Wick, Scott; Nakano, Takayuki; Kilinski, Lydia; Finer, Mitch; McArthur, James; Gyuris, Jeno
CORPORATE SOURCE: GPC Biotech, Inc., Cambridge, MA, 02139, USA
SOURCE: Journal of Molecular Medicine (Berlin) (2000), 78(8), 451-459
CODEN: JMLME8; ISSN: 0946-2716
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We describe the construction and characterization of a series of novel cyclin-dependent kinase inhibitors with increased antiproliferative activity for use in the genetic treatment of hyperproliferative cell disorders, such as angioplasty-induced restenosis. These inhibitors were generated through the fusion of truncated versions of the p27 gene to the full-length p16 gene. Biochem., the p27-p16 chimeric mols. were of comparable potency to the parental p27 in inhibiting the activities of several cyclin-dependent kinases in vitro. Replication-deficient adenoviruses encoding the parental p16, p27 genes, or their derivs. were created to assess the potency of the novel cyclin-dependent kinase inhibitor chimeric mols. to inhibit vascular **smooth muscle cell proliferation**, which is the seminal event in the restenosis process. One of the p27-p16 chimeric mols., W9, was obsd. to be the most potent inhibitor of human primary smooth muscle and endothelial cell **proliferation** when compared to the p16, p27, p27 derivs. or several alternative p27-p16 chimeric mols. Overexpression of the W9 chimeric mol. in human coronary artery smooth muscle cells induced human coronary artery **smooth muscle cell** growth arrest in G1 but did not induce cell apoptosis. Recombinant adenoviral vectors that express this W9 chimeric cyclin-dependent kinase inhibitor mol. constitute a novel potent antiproliferative agent for the **treatment** of **restenosis**.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:724230 HCAPLUS

DOCUMENT NUMBER: 134:293568
TITLE: Significance of p27 mRNA and protein expression in osteoplastic tumors
AUTHOR(S): Wen, Bin; Qin, Jushi; Li, Yang
CORPORATE SOURCE: Department of Pathology, Sun Yat-sen University of Medical Sciences, Canton, 510080, Peop. Rep. China
SOURCE: Zhongguo Zhongliu Linchang (2000), 27(6), 414-417
CODEN: ZZLIEP; ISSN: 1000-8179
PUBLISHER: Zhongguo Zhongliu Linchang Bianji Weiyuanhui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Objective: To evaluate the significance of p27 mRNA and protein expression in various kinds of osteoplastic tumors. Methods: Immunohistochem. and nonradioactive in situ hybridization methods were used to detect the expression of p27 mRNA and protein in 58 cases of osteoplastic tumors. Results: The pos. rate of p27 protein was 100% in osteoma, 87. 5% in osteoblastoma, 62. 8% in osteosarcoma. In addn., the nuclear staining of p27 was noted 85. 7% (6/7) in osteoma, 75% (6/8) in osteoblastoma, but only 4. 7% (2/43) in osteosarcoma. The results showed a statistical significance between benign tumors and osteosarcoma ($P < 0.01$) . The expression of p27 protein in osteosarcoma was significantly correlated with the invasiveness, relapse and **metastasis** of tumor. In situ hybridization, it revealed that there was no difference of expression levels of p27 mRNA between benign tumors and osteosarcoma and there was no statistical significance between p27 mRNA expression and its histol. types, differentiation, degree and biol. behavior of osteosarcoma. Conclusion: p27 protein has practical value in diagnosis of osteosarcoma, and it may serve as a new biol. indicator to predict the prognosis of the patient with osteosarcoma. Loss of p27 protein of osteosarcoma may be resulted from a posttranscriptional specific proteosome-mediated degrdn.

L10 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:628264 HCAPLUS
DOCUMENT NUMBER: 133:218484
TITLE: Inhibiting **proliferation** of smooth muscle cells with adenoviral or lentiviral vectors encoding cyclin dependent kinase inhibitors
INVENTOR(S): McArthur, James; Gyuris, Jeno; Finer, Mitchell
PATENT ASSIGNEE(S): Cell Genesys, Inc., USA; Mitotix, Inc.
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052159	A1	20000908	WO 2000-US4971	20000228
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1157108	A1	20011128	EP 2000-914723	20000228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: US 1999-122974P P 19990301
US 1999-163682P P 19991105
US 1999-457568 A 19991209
WO 2000-US4971 W 20000228

AB Disclosed are methods for using .DELTA.E1/.DELTA.E4 recombinant adenoviruses encoding cyclin dependent kinase inhibitors for inhibiting **smooth muscle cell proliferation.** Also disclosed are recombinant lentiviruses encoding cyclin dependent kinase inhibitors. Thus, cDNAs encoding 12-178-human p27INK and 25-93-human p27INK as well as fusions of these two proteins with human p16CIP/KIP were prepd. Adenoviruses contg. the cDNA for the fusion protein displayed smooth muscle **proliferation**-inhibiting activity in balloon-injured rabbit carotid arteries.

IT **157908-85-5**
RL: PRP (Properties)
(Unclaimed; inhibiting **proliferation** of smooth muscle cells with adenoviral or lentiviral vectors encoding cyclin dependent kinase inhibitors)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:621970 HCAPLUS
DOCUMENT NUMBER: 134:312
TITLE: eNOS gene transfer to vascular smooth muscle cells inhibits cell **proliferation** via upregulation of p27 and p21 and not apoptosis
AUTHOR(S): Sato, J.; Nair, K.; Hiddinga, J.; Eberhardt, N. L.; Fitzpatrick, L. A.; Katusic, Z. S.; O'Brien, T.
CORPORATE SOURCE: Department of Endocrinology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SOURCE: Cardiovascular Research (2000), 47(4), 697-706
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: **Smooth muscle cell** (**SMC**) **proliferation** is a crit. component of vascular diseases such as atherosclerosis and restenosis. Nitric oxide (NO) donors and gene transfer of endothelial nitric oxide synthase (eNOS) have been shown to inhibit **SMC proliferation.** NO may cause this effect by delaying cell cycle progression and/or induction of apoptosis. The aim of the current study was to examine the mechanism of eNOS-mediated inhibition of **SMC proliferation.** In addn., the effect of eNOS expression in vascular SMCs on the expression of the **cyclin dependent kinase** inhibitors, **p27** and p21 was examd. Methods: SMCs were transduced with an adenoviral vector encoding eNOS (AdeNOS) or .beta.-galactosidase (Ad.beta.Gal) at a multiplicity of infection of 100. Non-transduced cells served as addnl. controls. Transgene expression was sought by NADPH diaphorase staining, immunohistochem. and Western Blotting. Functionality of the recombinant protein was assessed by measurement of cGMP. Cell cycle anal. was performed by flow cytometry and p27 and p21 expression were studied by western blot anal. Apoptosis was sought by Annexin V staining and DNA laddering. Results: eNOS expression was detected in transduced SMCs. cGMP levels were increased in eNOS-transduced compared to control cells. Expression of eNOS in SMCs resulted in a delay in cell cycle progression and upregulation of p27 and p21. There was no increase in apoptosis detected in eNOS transduced cells after 24 or 72 h.

Conclusion: eNOS gene transfer to vascular SMCs inhibits cell **proliferation** via upregulation of p27 and p21 resulting in a delay in cell cycle progression.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:621964 HCAPLUS
DOCUMENT NUMBER: 133:332521
TITLE: eNOS inhibition of **proliferation**: a role for p21Sdi1/Cip1/Waf1 and p27Kip1
AUTHOR(S): Holt, C. M.
CORPORATE SOURCE: Cardiovascular Research Group, Clinical Sciences Centre, Northern General Hospital, Sheffield, S5 7AU, UK
SOURCE: Cardiovascular Research (2000), 47(4), 640-641
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 16 refs., focusing on the role of **cyclin-dependent kinase** inhibitors, **p27** and p21, in endothelial nitric oxide synthase (eNOS)-induced inhibition of vascular **smooth muscle cell proliferation**.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:597753 HCAPLUS
DOCUMENT NUMBER: 133:261178
TITLE: Cell cycle arrest and apoptosis of melanoma cells by docosahexaenoic acid: association with decreased pRb phosphorylation
AUTHOR(S): Albino, Anthony P.; Juan, Gloria; Traganos, Frank; Reinhart, Lisa; Connolly, Jeanne; Rose, David P.; Darzynkiewicz, Zbigniew
CORPORATE SOURCE: The American Health Foundation, Valhalla, NY, 10595, USA
SOURCE: Cancer Research (2000), 60(15), 4139-4145
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The incidence of cutaneous malignant melanoma is undergoing a dramatic increase in persons with light-color skin in all parts of the world. The prognosis for individuals with advanced disease is dismal due to the lack of effective treatment options. Thus, there is a need for new approaches to control tumor progression. Epidemiol., exptl., and mechanistic data implicate .omega.-6 polyunsatd. fatty acids (PUFAs) as stimulators and long-chain .omega.-3 PUFAs as inhibitors of development and progression of a range of human cancers, including melanoma. The aim of this study was to assess the mechanisms by which docosahexaenoic acid (DHA), an .omega.-3 PUFA, affects human melanoma cells. Exponentially growing melanoma cell lines were exposed in vitro to DHA and then assessed for (a) inhibition of cell growth; (b) expression of cyclins and cyclin-dependent kinase inhibitors in individual cells by flow cytometry and immunocytochem. using specific monoclonal antibodies to cyclin D1, cyclin E, p21WAF1/CIP1, or p27KIP1; and (c) expression of total pRbT independent of phosphorylation state and hypophosphorylated pRbP- in fixed cells by flow cytometry and immunocytochem. using specific monoclonal antibodies to pRbT or pRbP-,

resp. After treatment with increasing concns. of DHA, cell growth in a majority of melanoma cell lines (7 of 12) was inhibited, whereas in 5 of 12 cell lines, cell growth was minimally affected. Two melanoma cell lines were examd. in detail, one resistant (SK-Mel-29) and one sensitive (SK-Mel-110) to the inhibitory activity of DHA. SK-Mel-29 cells were unaffected by treatment with up to 2 .mu.g/mL DHA whether grown in the absence or presence of 1% fetal bovine serum (FBS). No appreciable change was obsd. in cell growth, cell cycle distribution, the status of pRb phosphorylation, cyclin D1 expression, or the levels of the **cyclin -dependent kinase** inhibitors p21 and **p27**.
In contrast, SK-Mel-110 cell growth was inhibited by DHA with the cells accumulating either in G1 or S phase: 0% in SK-Mel-29 vs. 13.3 or 41.2% in SK-Mel-110 in the absence or presence of FBS, resp. In the absence of serum, considerable death occurred by apoptosis. In addn., DHA treatment resulted in increasing nos. of SK-Mel-110 cells (from 12 to >40%) expressing hypophosphorylated pRb, whereas the levels of cyclin D1 and p21 changed little. Expression of p27 in these cells increased >2.5 times when grown in the absence of FBS but not in the presence of 1% FBS. Thus, we show for the first time that DHA inhibits the growth of cultured **metastatic** melanoma cells. Furthermore, growth inhibition correlates with a quant. increase in hypophosphorylated pRb in the representative sensitive melanoma cell line SK-Mel-110. Although multiple factors influence pRb phosphorylation, it appears that both cyclin D1 and p21 expression do not change in the presence of DHA, although p27 was strikingly increased in SK-Mel-110 cells in the absence of FBS. The fact that pRb became hypophosphorylated after exposure to DHA suggests a cross-talk mechanism between fatty acid metab. and the pRb pathway. Detg. the mechanism by which PUFAs can inhibit melanoma growth will be an important first step in the rational use of PUFAs as antitumor agents.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:592335 HCAPLUS
DOCUMENT NUMBER: 134:98756
TITLE: Decreased expression of p27 protein is associated with advanced tumor stage in hepatocellular carcinoma
AUTHOR(S): Tannapfel, Andrea; Grund, Dorothee; Katalinic, Alexander; Uhlmann, Dirk; Kockerling, Ferdinand; Haugwitz, Ulrike; Wasner, Mark; Hauss, Johann; Engeland, Kurt; Wittekind, Christian
CORPORATE SOURCE: Institute of Pathology, University of Leipzig, Leipzig, 04103, Germany
SOURCE: International Journal of Cancer (2000), 89(4), 350-355
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reduced expression of the **cyclin-dependent kinase** inhibitor **p27** has previously been correlated with fatal clin. outcome in some tumors, including gastric, breast, and prostate cancers. For hepatocellular carcinoma, the findings are equivocal. In situ hybridization and immunohistochem. were performed on a series of 203 curatively (R0) resected hepatocellular carcinomas and in corresponding non-cancerous liver tissue to detect p27. Patients receiving liver transplantation were excluded. The results were correlated with histopathol. stage according to the UICC system, Edmondson grade, several other histopathol. factors of possible prognostic significance, and finally patient survival. Whereas p27 mRNA was expressed homogeneously in all carcinomas examd., the p27 protein was

found in various amts. The labeling index of p27 protein was significantly lower in advanced stages of the disease (P < 0.001, .chi.2 = 28.1). We obsd. decreased p27 protein in higher pT categories (P < 0.001, .chi.2 = 24.7) and in multiple tumor nodules (P < 0.001, .chi.2 = 9.3). Multivariate Cox survival anal. identified age, co-existing cirrhosis, and Edmondson grade as independent prognostic factors. We conclude that evaluation of p27 in hepatocellular carcinoma is useful to predict stage of disease and may have clin. significance, e.g., in predicting optimal therapeutic regimes.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:591375 HCAPLUS
DOCUMENT NUMBER: 134:98742
TITLE: p27kip1 protein expression correlates with survival in myxoid and round-cell liposarcomas
AUTHOR(S): Oliveira, Andre M.; Nascimento, Antonio G.; Okuno, Scott H.; Lloyd, Ricardo V.
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, 55905, USA
SOURCE: Journal of Clinical Oncology (2000), 18(15), 2888-2893
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: The p27kip1 protein (**p27**) is a **cyclin-dependent kinase** inhibitor that has been shown to be an independent prognostic factor in a variety of human neoplasms. Low expression of p27 tends to occur in more aggressive neoplasms. The role of p27 as an independent prognostic factor in the spectrum of myxoid and round-cell liposarcomas has not been examd. Materials and Methods: Forty-seven cases of myxoid and round-cell liposarcomas were examd. Ki-67 antigenClinicopathol. features and immunohistochem. expression of p27 and Ki-67 antigen were studied in all cases. Survival anal. was performed using the logrank test and the Cox multivariate regression model. Results: The male:female ratio was 1.4:1, and the mean age at diagnosis was 45 yr. The tumors were located in the lower extremities (94%) and retroperitoneum (6%). The median tumor size was 13.5 cm. The median follow-up was 6.3 yr, and the overall 5- and 10-yr survival rates were 76% and 67%, resp. Low expression of p27 was identified in 34 cases (72%) and correlated with decreased **metastasis**-free (P = .026) and overall survival (P = .008). In a multi-variate anal., only round-cell differentiation and low expression of p27 independently predicted decreased **metastasis**-free and overall survival. Conclusion: p27 expression predicts the clin. behavior of myxoid and round-cell liposarcomas, even in neoplasms with few or no round-cell differentiation.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:279449 HCAPLUS
DOCUMENT NUMBER: 133:175481
TITLE: Expression and clinical significance of the G1-S modulators in carcinoma of the extrahepatic bile duct
AUTHOR(S): Ito, Yasuhiro; Takeda, Tsutomu; Sakon, Masato; Monden, Morito; Tsujimoto, Masahiko; Matsuura, Nariaki
CORPORATE SOURCE: Department of Surgery, Osaka Seamen's Insurance Hospital, Osaka, 552-0021, Japan
SOURCE: Anticancer Research (2000), 20(1A), 337-344

CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of cell cycle modulators at the G1-S boundary, the retinoblastoma gene product (pRb), p21, p16, p27, p53, cyclin D1 as well as Ki-67 was investigated with 39 extrahepatic bile duct carcinomas (BDC). The Ki-67 labeling index (LI) was higher in cases with poor differentiation, lymph node **metastasis** and stage III or IV. Cyclin D1 overexpression was seen in 14 cases (35.8%). This phenomenon could be obsd. more frequently in cases of hilar carcinoma and with poor differentiation, perineural invasion, lymphatic invasion and lymph node **metastasis**. Furthermore, Ki-67 LI was higher in cyclin D1 overexpressing cases. P27 expression showed inverse relationships with Ki-67 LI, lymph node **metastasis** and aberrant p53 expression. Although p16 and p21 expression significantly correlated with lymph node **metastasis** and cyclin D1 overexpression, resp., they were not related to Ki-67 LI. PRb expression was obsd. in all cases. Although the LI was lower in carcinoma of upper and middle bile ducts, no correlation was established between pRb expression and other clinicopathol. parameters including Ki-67 LI. Aberrant p53 expression was obsd. in 13 cases (33.3%) and Ki-67 LI was significantly higher in these cases. These findings suggest that p27 and cyclin D1 strongly correlate with BDC proliferation and reflect the biol. aggressiveness of this carcinoma.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:192975 HCAPLUS
DOCUMENT NUMBER: 132:306243
TITLE: Physiological cyclic stretch causes cell cycle arrest in cultured vascular smooth muscle cells
AUTHOR(S): Chapman, Gary B.; Durante, William; Hellums, J. David; Schafer, Andrew I.
CORPORATE SOURCE: Department of Bioengineering, Rice University, Houston, TX, 77005, USA
SOURCE: American Journal of Physiology (2000), 278(3, Pt. 2), H748-H754
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Smooth muscle cells (**SMC**) are the major cellular component of the blood vessel wall and are continuously exposed to cyclic stretch due to pulsatile blood flow. This study examd. the effects of a physiol. relevant level of cyclic stretch on rat aortic vascular **SMC** **proliferation**. Treatment of static **SMC** with serum, platelet-derived growth factor, or thrombin stimulated **SMC** **proliferation**, whereas exposure of **SMC** to cyclic stretch blocked the **proliferative** effect of these growth factors. The stretch-mediated inhibition in **SMC** growth was not due to cell detachment or increased cell death. Flow cytometry anal. revealed that cyclic stretch increased the fraction of **SMC** in the G0/G1 phase of the cell cycle. Stretch-inhibited G1/S phase transition was assocd. with a decrease in retinoblastoma protein phosphorylation and with a selective increase in the **cyclin-dependent** **kinase** inhibitor p21, but not **p27**. These results demonstrate that cyclic stretch inhibits **SMC** growth by blocking cell cycle progression and suggest that physiol. levels of cyclic stretch contribute to vascular homeostasis by inhibiting the **proliferative**

pathway of **SMC**.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:122926 HCAPLUS
DOCUMENT NUMBER: 133:37972
TITLE: Apigenin inhibits endothelial-cell **proliferation** in G2/M phase whereas it stimulates smooth-muscle cells by inhibiting p21 and p27 expression
AUTHOR(S): Trochon, Veronique; Blot, Emmanuel; Cymbalista, Florence; Engelmann, Carsten; Tang, Ruo-Ping; Thomaidis, Annick; Vasse, Marc; Soria, Jeannette; Lu, He; Soria, Claudine
CORPORATE SOURCE: Institut d'Hematologie, Hopital Saint-Louis, Paris, F-75475, Fr.
SOURCE: International Journal of Cancer (2000), 85(5), 691-696
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apigenin is a plant flavonoid that is thought to play a role in the prevention of carcinogenesis. However, its mechanism of action has not yet been elucidated. Because of the importance of angiogenesis in tumor growth, the authors investigated the effect of apigenin on endothelial and smooth-muscle cells in an in vitro model. Apigenin markedly inhibited the **proliferation**, and, to a lesser degree, the **migration** of endothelial cells, and capillary formation in vitro, independently of its inhibition of hyaluronidase activity. In contrast, it strongly stimulated vascular **smooth-muscle-cell proliferation**. The mol. mechanisms of apigenin activity were analyzed in these 2 types of cells. The results show that apigenin inhibits endothelial-cell **proliferation** by blocking the cells in the G2/M phase as a result of the accumulation of the hyperphosphorylated form of the retinoblastoma protein. Apigenin stimulation of smooth-muscle cells was attributed to the reduced expression of 2 **cyclin-dependent kinase** inhibitors, p21 and **p27**, which neg. regulate the G1-phase cyclin-dependent kinase.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:811928 HCAPLUS
DOCUMENT NUMBER: 132:263232
TITLE: p27 cell-cycle inhibitor is inversely correlated with lymph node **metastases** in right-sided colon cancer
AUTHOR(S): Liu, Dong Feng; Ferguson, Kelly; Cooper, Gregory S.; Grady, William M.; Willis, Joseph
CORPORATE SOURCE: Department of Pathology, University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, USA
SOURCE: Journal of Clinical Laboratory Analysis (1999), 13(6), 291-295
CODEN: JCANEM; ISSN: 0887-8013
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **P27**, a **cyclin-dependent kinase**

inhibitor, suppresses proliferation of normal and neoplastic cells. Expression of p27 is correlated with survival in colon cancer. To some degree, right-sided colon cancers differ biol. and clin. from left-sided colon cancers. We analyzed 41 patients with right-sided colon cancers, including 18 cases with regional lymph node **metastases** and 23 cases with neg. lymph node. Immunostaining for p27 was performed on histol. sections of primary cancers and scored. Decreased p27 protein expression was assocd. with large tumor size. As percentages of pos. stained tumor cells decreased from 70 to 29%, the mean tumor size increased from 1.9 to 7.3 cm. P27 protein expression significantly decreased in primary cancers with angiolymphatic invasion or with pos. lymph nodes in comparison with those without angiolymphatic invasion or with neg. lymph nodes. P27 expression was not statistically different in terms of depth of tumor invasion (T1/T2 vs. T3/T4), tumor type or tumor differentiation. Low p27 expression in primary cancers was correlated with lymph node **metastases**. However, it did not correlate with any other histol. parameters. In summary, decreased p27 expression was assocd. with an increased likelihood of lymph node **metastases** in colon cancers, independent of depth of tumor invasion. This implies that p27 is a potentially important predictor for tumor **metastasis** and patient's prognosis in right-sided colon cancers.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:811273 HCAPLUS
DOCUMENT NUMBER: 132:49035
TITLE: Interaction of p27(Kip1) with FKBP-12
INVENTOR(S): Nandabalan, Krishnan; Yang, Meijia
PATENT ASSIGNEE(S): Curagen Corporation, USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9965939	A1	19991223	WO 1999-US13659	19990618
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9946904	A1	20000105	AU 1999-46904	19990618
EP 1087994	A1	20010404	EP 1999-930350	19990618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-99857 A2 19980618
WO 1999-US13659 W 19990618

AB The present invention discloses an interaction between p27(Kip1) and FKBP-12 and the formation of a p27(Kip1)-FKBP-12 complex, or of the derivs., fragments, analogs and homologs thereof, that were identified using a modified, improved yeast two hybrid assay system. The assay system involves the use of antibody against the complex, and nucleic acid

probes or primers. Methodologies of screening these aforementioned complexes for efficacy in treating and/or preventing various diseases and disorders, particularly hyperproliferative disorders, including, but not limited to, atherosclerosis, cancer or proliferative disorder, neurodegenerative disease, autoimmune disease, membrane nephropathy disorders, and viral infection, are also disclosed herein.

IT **157908-85-5**
RL: PRP (Properties)
(amino acid sequence; antibody and DNA probes or primers for detecting p27(Kip1)-FKBP-12 complexes and efficacy of treatment and prevention of related diseases)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:642329 HCAPLUS
DOCUMENT NUMBER: 132:62221
TITLE: Expression of **cyclin dependent kinase** inhibitor **p27** during **proliferation** in vascular **smooth muscle cell**
AUTHOR(S): Yuan, Yong; Xu, Ding-Li; Liu, Yi-Li; Jia, Man-Ying
CORPORATE SOURCE: Nanfang Hospital, The First Military Medical University, Canton, 510515, Peop. Rep. China
SOURCE: Shengli Xuebao (1999), 51(3), 285-290
CODEN: SLHPAH; ISSN: 0371-0874
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB This study was to investigate cell cycle distribution of the vascular smooth muscle cells (VSMCs) and neg. regulator of cell **proliferation** p27 expression caused by platelet derived growth factor BB (PDGF-BB), angiotensin II (Ang II) and arginine vasopressin (AVP). Deprived of fetal calf serum for 48 h, cultured VSMCs in quiescent condition were collected at different times after stimulation of Ang II, AVP and PDGF-BB. Cell cycle distribution and p27 expression were detd. with a flow cytometer. The results showed that the protein content of VSMCs was significantly increased (43.6%) by Ang II as a result of hypertrophy, but Ang II did not lead to downregulation of p27. AVP downregulated p27 slightly. PDGF inhibited p27 expression significantly and cause VSMCs hyperplasia. These results suggest that the progression of VSMCs through G1 to S phase might be brought out by the inhibition of p27 during **proliferation**.

L10 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:547692 HCAPLUS
DOCUMENT NUMBER: 131:270063
TITLE: Cell cycle arrest and inhibition of anoikis by galectin-3 in human breast epithelial cells
AUTHOR(S): Kim, Hyeong-Reh Choi; Lin, Huei-Min; Biliran, Hector; Raz, Avraham
CORPORATE SOURCE: Department of Pathology, Breast Cancer Program, Karmanos Cancer Institute, School of Medicine, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Cancer Research (1999), 59(16), 4148-4154
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Galectin-3 is a member of a growing family of animal .beta.-galactoside-

binding proteins shown to be involved in cell growth, differentiation, apoptosis resistance, and tumor progression. In the present study, we investigated whether galectin-3 can protect against apoptosis induced by the loss of cell anchorage (anoikis). Because studies suggest that cellular sensitivity to anoikis is assocd. with cell cycle regulation, we examd. the role of galectin-3 on cell cycle regulation. Although BT549 cells (human breast epithelial cells) undergo anoikis, galectin-3-overexpressing BT549 cells respond to the loss of cell adhesion by inducing G1 arrest without detectable cell death. Galectin-3-mediated G1 arrest involves down-regulation of G1-S cyclin levels (cyclin E and cyclin A) and upregulation of their inhibitory protein levels (p21WAF1/CIP1 and p27KIP1). After the loss of cell anchorage, Rb protein becomes hypophosphorylated in galectin-3-overexpressing cells, as predicted from the flow cytometric anal. and immunoblot anal. of cyclins and their inhibitors. Interestingly, galectin-3 induces cyclin D1 expression (an early G1 cyclin) and its assocd. kinase activity in the absence of cell anchorage. On the basis of these results, we propose that galectin-3 inhibition of anoikis involves cell cycle arrest at an anoikis-insensitive point (late G1) through modulation of gene expression and activities of cell cycle regulators. The present study suggests that galectin-3 may be a crit. determinant for anchorage-independent cell survival of disseminating cancer cells in the circulation during **metastasis**.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:536648 HCAPLUS
DOCUMENT NUMBER: 131:280832
TITLE: Cancer chemoprevention by tea polyphenols through mitotic signal transduction blockade
AUTHOR(S): Lin, Jen-Kun; Liang, Yu-Chih; Lin-Shiau, Shoei-Yn
CORPORATE SOURCE: Institute of Biochemistry, National Taiwan University, Taipei, Taiwan
SOURCE: Biochemical Pharmacology (1999), 58(6), 911-915
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 28 refs. Tea is a popular beverage. The consumption of green tea is assocd. with a lower risk of several types of cancer, including stomach, esophagus, and lung. The cancer chemopreventive effect of tea has been attributed to its major phytopolyphenols. The tea polyphenols comprise about one-third of the wt. of the dried leaf, and they show profound biochem. and pharmacol. activities including antioxidant activities, modulation of carcinogen metab., inhibition of cell proliferation, induction of cell apoptosis, and cell cycle arrest. They intervene in the biochem. and mol. processes of multistep carcinogenesis, comprising tumor initiation, promotion, and progression. Several studies demonstrate that most tea polyphenols exert their scavenging effects against reactive oxygen species (ROS); excessive prodn. of ROS has been implicated for the development of **cardiovascular diseases**, neurodegenerative disorders, and cancer. Recently, we have found that the major tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) suppresses extracellular signals and cell proliferation through epidermal growth factor receptor binding in human A431 epidermoid carcinoma cells; EGCG also blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of the transcription factor NF.kappa.B in macrophages. Furthermore, EGCG blocks the cell cycle at the G1 phase in MCF-7 cells. We have demonstrated that

EGCG inhibits the activities of cyclin-dependent kinases 2 and 4; meanwhile, EGCG induces the expression of the **Cdk** inhibitors p21 and **p27**. These results suggest that tumor promotion can be enhanced by ROS and oxidative mitotic signal transduction, and this enhancement can be suppressed by EGCG or other tea polyphenols.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:420297 HCAPLUS
DOCUMENT NUMBER: 131:197742
TITLE: Expression of p27 is associated with Bax expression and spontaneous apoptosis in oral and oropharyngeal carcinoma
AUTHOR(S): Fujieda, Shigeharu; Inuzuka, Manabu; Tanaka, Nobuyuki; Sunaga, Hiroshi; Fan, Guo-Kang; Ito, Toshihisa; Sugimoto, Chizuru; Tsuzuki, Hideaki; Saito, Hitoshi
CORPORATE SOURCE: Dep. Otorhinolaryngology, Fukui Medical Univ., Fukui, Japan
SOURCE: International Journal of Cancer (1999), 84(3), 315-320
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB P27Kipl, a cyclin-dependent kinase inhibitor, is a neg. regulator of the cell cycle, and apoptosis is a genetically encoded program of cell death. To clarify the relation between the cell cycle and apoptosis, the authors investigated expression of p27, cyclin DI, and apoptosis-related proteins (p53, Bax, Bcl-2 and c-Myc) in 60 cases of oral and oropharyngeal squamous-cell carcinomas (SCC) using an immunohistochem. approach, and evaluated spontaneous apoptosis in vivo. The authors' most notable finding was that spontaneous apoptosis in the p27-pos. group was higher than that in the p27-neg. group. In addn., the percentage of p27-pos. cells was clearly correlated with that of Bax-pos. cells and with that of cyclin DI-pos. cells. Expression of p27 was inversely assocd. with the clin. stage of total tumor progression. However, no correlation was found between p27 expression and the following parameters: gender, tumor size, lymph node **metastasis**, overall survival, and disease-free survival. Evidently, the action of the cell-cycle regulator p27 is closely linked with apoptosis in clin. samples from patients, and over-expression of p27 might induce apoptosis in cancer cells through elevation of Bax expression, thereby acting on tumor progression.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:341388 HCAPLUS
DOCUMENT NUMBER: 131:100479
TITLE: Dissociation between grow arrest and differentiation in Caco-2 subclone expressing high levels of sucrase
AUTHOR(S): Tian, Jean Q.; Quaroni, Andrea
CORPORATE SOURCE: Section of Physiology, Cornell University, Ithaca, NY, 14853, USA
SOURCE: American Journal of Physiology (1999), 276(5, Pt. 1), G1094-G1104
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Growth arrest and cell differentiation are generally considered temporally

and functionally linked phenomena in small intestinal crypt cells and colon **tumor cell** lines (Caco-2, HT-29). The authors have derived a Caco-2 subclone (NGI3) that deviates from such a paradigm. In striking contrast with the parental cells, **proliferative** and subconfluent NGI3 cells were found to express sucrase-isomaltase (SI) mRNA and to synthesize relatively high levels of SI, dipeptidyl peptidase IV, and aminopeptidase N (APN). In postconfluent cells, little difference was seen in SI mRNA levels between Caco-2 and NGI3 cells, but the latter still expressed much higher levels of SI that could be attributed to higher rates of translation. APN expression was also greatly enhanced in NGI3 cells. To det. whether high levels of brush-border enzymes correlated with expression of cell-cycle regulatory proteins, the authors investigated their relative cellular levels in growing and growth-arrested cells. The results showed that the **cyclin-dependent kinase** inhibitors (p21 and **p27**) and D-type cyclins (D1 and D3) were all induced in postconfluent cells, but NGI3 cells expressed much higher levels of p21. This study demonstrated that cell growth and expression of differentiated traits are not mutually exclusive in intestinal epithelial cells and provided evidence indicating that posttranscriptional events play an important role in regulation of SI expression.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:341278 HCAPLUS
DOCUMENT NUMBER: 131:97925
TITLE: NOS gene transfer inhibits expression of cell cycle regulatory molecules in vascular smooth muscle cells
AUTHOR(S): Sharma, Ram V.; Tan, Enqing; Fang, Shengyun; Gurjar, Milind V.; Bhalla, Ramesh C.
CORPORATE SOURCE: Department of Anatomy and Cell Biology and The Cardiovascular Center, The University of Iowa College of Medicine, Iowa City, IA, 52242, USA
SOURCE: American Journal of Physiology (1999), 276(5, Pt. 2), H1450-H1459
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanisms of nitric oxide (NO)-mediated inhibition of vascular smooth muscle (VSM) cell **proliferation** are still obscure. Cyclins A and E in assocn. with cyclin-dependent kinase 2 (cdk2) serve as pos. regulators for mammalian cell cycle progression through the G1/S checkpoint of the cell cycle and subsequent cell **proliferation**. Therefore, the authors have tested the effect of adenovirus-mediated transfection of the endothelial nitric oxide synthase (eNOS) gene into guinea pig coronary VSM cells on platelet-derived growth factor (BB homodimer) (PDGF-BB)-stimulated cell **proliferation** and the expression of cell cycle regulatory mols. Transfection of the eNOS gene (eNOS) into VSM cells significantly inhibited [3H]thymidine incorporation into the DNA in response to PDGF-BB stimulation compared with lacZ-transfected control cells. The eNOS transfer significantly inhibited PDGF-BB-induced **proliferating** cell nuclear antigen (PCNA) and cyclin A expression in VSM cells compared with cells transfected with the control vector. The time course of cyclin E expression in response to PDGF-BB stimulation was delayed in eNOS-transfected cells. Levels of **cyclin-dependent kinase** inhibitors p21 and **p27** were not significantly affected by eNOS transfer. The eNOS transfer did not decrease PDGF-3 receptor no., affinity, and

autophosphorylation measured by radioreceptor assay and Western anal. These results suggest that inhibition of PDGF-stimulated expression of cyclin A, cyclin E, and PCNA is the target of NO action. These findings could explain, at least in part, NO-mediated inhibition of VSM cell **proliferation.**

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:164487 HCAPLUS
DOCUMENT NUMBER: 131:16875
TITLE: Heparin inhibits **proliferation** of myometrial and leiomyomal smooth muscle cells through the induction of .alpha.-smooth muscle actin, calponin h1 and p27
AUTHOR(S): Horiuchi, Akiko; Nikaido, Toshio; Ya-Li, Zhai; Ito, Kazuko; Orii, Ayaka; Fujii, Shingo
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Matsumoto, 390-8621, Japan
SOURCE: Molecular Human Reproduction (1999), 5(2), 139-145
CODEN: MHREFD; ISSN: 1360-9947
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mast cells are widely distributed in human tissues, including the human uterus. However, the function of mast cells in uterine smooth muscle has not been clearly established. Mast cells possess secretory granules contg. such substances as heparin, serotonin, histamine and many cytokines. To help establish the role of mast cells in the human myometrium, the action of heparin was investigated using smooth muscle cells (**SMC**) from normal myometrium and from leiomyoma. The **proliferation** of cultured myometrial and leiomyomal **SMC** was inhibited by heparin treatment. Flow cytometric anal. showed that the population in the G1 phase of the cell cycle increased under heparin treatment. Western blotting anal. showed that markers of **SMC** differentiation such as .alpha.-smooth muscle actin (.alpha.-SMA), calponin h1 and **cyclin-dependent kinase** inhibitor **p27** were induced by heparin, whereas cell-cycle-related gene products from the G1 phase of the cell cycle, such as cyclin E and cdk2, were not changed. Taken together, these results indicate that heparin inhibits the **proliferation** of myometrial and leiomyomal **SMC** through the induction of .alpha.-SMA, calponin h1 and p27. The authors suggest that heparin from mast cells may induce differentiation in uterine **SMC** and may influence tissue remodelling and reconstruction during physiol. and pathophysiol. events.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:113792 HCAPLUS
DOCUMENT NUMBER: 130:179312
TITLE: Fusion proteins comprising cyclin-dependent kinase-binding modules as inhibitors of cell-cycle progression
INVENTOR(S): Gyuris, Jeno; Lamphere, Lou; Beach, David H.
PATENT ASSIGNEE(S): Mitotix, Inc., USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906540	A2	19990211	WO 1998-US15759	19980729
WO 9906540	A3	19991216		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9886014	A1	19990222	AU 1998-86014	19980729
EP 1000166	A2	20000517	EP 1998-937264	19980729
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001512008	T2	20010821	JP 2000-505282	19980729

PRIORITY APPLN. INFO.: US 1997-902572 A2 19970729
WO 1998-US15759 W 19980729

AB The present invention pertains to novel inhibitors of cyclin-dependent kinases (CDKs), particularly CDK/cyclin complexes, which inhibitors can be used to control proliferation and/or differentiation of cells in which the inhibitors are introduced. Transfection systems are described expressing a fusion protein contg. an inhibitor polypeptide comprising cyclin-dependent kinase (CDK)-binding motifs from more than one protein and, optionally, an endothelialization polypeptide such as the HIV-1 tat protein. Fusion proteins and their encoding nucleic acid sequences are provided for **p27** and p16, INK4 proteins contg. **CDK** -binding motifs, and for tat fragments fused to p27 and/or p16. These fusion proteins successfully inhibit Cdk2/cyclin E, Cdk4/Cyclin D1, and Cdc2/cyclinB with IC50 values in the nanomolar range.

L10 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:616476 HCAPLUS
DOCUMENT NUMBER: 130:36472
TITLE: Down-regulation of p27 is associated with development of colorectal adenocarcinoma **metastases**
AUTHOR(S): Thomas, George V.; Szigeti, Kinga; Murphy, Michael; Draetta, Giulio; Pagano, Michele; Loda, Massimo
CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA
SOURCE: American Journal of Pathology (1998), 153(3), 681-687
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **cyclin-dependent kinase** inhibitor **p27** is a neg. regulator of the cell cycle and a potential tumor suppressor gene. Because we had previously demonstrated that loss of p27 protein is assocd. with aggressive behavior in colorectal adenocarcinomas, we used immunohistochem. and in situ hybridization to evaluate the potential role of alterations in p27 expression in primary and **metastatic** colorectal adenocarcinomas. Parallel immunostaining was performed for Ki-67 and p53. We evaluated 13 cases of metachronous and 23 cases of synchronous primary and **metastatic** colorectal tumor pairs. In the synchronous subgroup (Stage IV tumors), 57% of the

primary tumor and **metastases** pairs did not express p27 protein and the remainder were low expressors. In the metachronous subgroup, 54% of the primary tumors were low expressors and the remainder high expressors of p27 protein. There was a significant redn. in the expression of p27 in the metachronous **metastases** (mean pos. cells: 14.5%) when compared to the corresponding primary tumors (mean pos. cells: 41.8%). All the primary and **metastatic** tumors in the metachronous subgroup showed high levels of p27 mRNA expression. There was no assocn. between loss of p27 and either Ki-67 count or p53 expression. Because p27 is known to be up-regulated when epithelial cells are grown in suspension, the down-regulation of p27 in circulating tumor cells may confer the ability to grow in an environment of altered extracellular matrix or intercellular adhesion properties, two situations which may facilitate **metastases**.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 33 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:611643 HCAPLUS
DOCUMENT NUMBER: 130:2619
TITLE: Relationship of p53 overexpression to other cell cycle regulatory proteins in oral squamous cell carcinoma
AUTHOR(S): Warnakulasuriya, K. A. A. S.; Tavassoli, M.; Johnson, N. W.
CORPORATE SOURCE: The Department of Oral Medicine and Pathology, WHO Collaborating Centre for Oral Cancer and Precancer, King's College School of Medicine and Dentistry, London, SE5 9RW, UK
SOURCE: Journal of Oral Pathology & Medicine (1998), 27(8), 376-381
CODEN: JPMEEA; ISSN: 0904-2512
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aberrations of the p53 gene and the overexpression of its protein are described in a variety of neoplasms, including oral and other head and neck cancers. Here we report the assocn. of p53 (over)expression with a downstream cell cycle inhibitor p21/waf 1 in oral squamous cell carcinoma (SCC). The loss of expression of p16 and **p27**, two other **cyclin-dependent kinase** (**cdk**) inhibitors, was also examd. In this panel of tumors, 10/24 carcinomas were p53-immunopos. Heterogeneous expression of p21 and p27 was seen in 10/24 SCC and 9/16 SCC, resp., and this was not correlated to p53 status. The expression of p21 and p27 in these SCCs suggests the existence of mechanisms by which some growing tumor cells may tolerate these cell cycle inhibitors; eight SCCs lacked expression of both inhibitors but only two of these cancers overexpressed p53, suggesting that accumulation of p21/p27 can be independent of the functional status of the p53 gene. Data do not support a clear example of a phenotype that shows an overexpression of p53 with downregulation of p21 or p27 leading to cell cycle alterations. Furthermore, only three SCCs were p16-neg. and p53-pos. This suggests that these two tumor suppressors may act in sep. pathways.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:421263 HCAPLUS
DOCUMENT NUMBER: 129:197648
TITLE: Cell cycle-independent induction of apoptosis by the anti-tumor drug flavopiridol in endothelial cells

AUTHOR(S): Brusselbach, Sabine; Nettelbeck, Dirk M.; Sedlacek, Hans-Harald; Muller, Rolf
CORPORATE SOURCE: Institut fur Molekularbiologie und Tumorforschung (IMT), Philipps-Universitat Marburg, Marburg, D-35033, Germany
SOURCE: International Journal of Cancer (1998), 77(1), 146-152
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The anti-tumor drug Flavopiridol is a potent inhibitor of cyclin-dependent kinases (cdks). As a consequence, Flavopiridol-treated cells arrest in both G1 and G2, but Flavopiridol has also been shown to be cytotoxic for some **tumor cell** lines. The underlying mol. events are, however, unclear. We now show that Flavopiridol induces apoptosis in human umbilical vein endothelial cells (HUVECs), as judged by the occurrence of classical apoptotic markers, including chromatin condensation, internucleosomal cleavage, DNA fragmentation (TUNEL assay), annexin V binding and poly(ADP-ribose) polymerase (PARP)-cleavage. Such induction of apoptosis occurs with equal efficiency in both **proliferating** and G0/G1-arrested cells. Because growth-arrested HUVECs lack cdk2 activity and contain high levels of the **cdk** inhibitor **p27**, our observations suggest that cell cycle regulated cdks may not be the only crit. target for Flavopiridol-induced apoptosis. Surprisingly, A549 lung carcinoma cells were clearly dependent on cell **proliferation** for the induction of cell death, pointing to cell type-related differences in the mechanism of Flavopiridol action.

L10 ANSWER 35 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:273888 HCAPLUS
TITLE: Loss or altered subcellular localization of p27 in barrett's associated adenocarcinoma
AUTHOR(S): Singh, Surendra P.; Lipman, Jennifer; Goldman, Harvey; Ellis, F. Henry, Jr.; Aizenman, Laura; Cangi, M. Giulia; Signoretti, Sabina; Chiaur, Dah S.; Pagano, Michele; Loda, Massimo
CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, 02215, USA
SOURCE: Cancer Res. (1998), 58(8), 1730-1735
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **cyclin-dependent kinase** inhibitor **p27** is a neg. regulator of the cell division cycle. It is expressed at the highest levels during the quiescent (G0) and prereplicative (G1) phases, and its degrdn. is required for entry into the S phase. Because lack of p27 is assocd. with aggressive behavior in a variety of tumors of epithelial and lymphoid origin, we used immunohistochem. and in situ hybridization to evaluate the expression of p27 in metaplastic and dysplastic Barrett's epithelium and to assess its prognostic significance in barrett's assocd. adenocarcinoma (BAA) of the esophagus. In metaplastic Barrett's epithelium, p27 protein and mRNA were restricted to the superficial third of glands in all cases and extended to the lower third in 4 cases. In contrast, expression of p27 message and protein was both increased and full-thickness, in the 23 cases with high-grade dysplasia adjacent to BAA and in carcinoma in situ. Although all invasive carcinomas had elevated levels of p27 mRNA, 45 (83%) of 54 invasive carcinomas had low p27 protein levels (<50% pos. tumor cells).

Low p27 protein correlated with higher histol. grade (P < 0.0001), depth of invasion (P = 0.0120), presence of lymph node **metastasis** (P = 0.05), and survival (P = 0.0197). In addn. to the nuclear staining, cytoplasmic staining of p27 was noted in 11 of 23 (48%) of cases of dysplasia and in 14 of 54 (26%) adenocarcinomas and confirmed, in a subset of cases, by subcellular fractionation of protein lysates obtained from fresh tumor tissues. Cytoplasmic localization of p27 was also assocd. with decreased survival (P = 0.0239). Loss of p27 conferred poor prognosis independently of proliferative index, as assessed by Ki-67 (MIB-1) immunostaining, which was not significantly different in survivors vs. nonsurvivors. These results show that: (a) distribution of p27 message and protein parallel one another in metaplastic and dysplastic Barrett's epithelium, suggesting transcriptional regulation of the gene in the nonneoplastic setting; (b) p27 is inactivated in the majority of BAA as a result of either post-transcriptional modification or altered subcellular localization; and (c) loss of the cell cycle inhibitor p27 is assocd. with parameters of aggressive behavior and unfavorable outcome in BAA.

L10 ANSWER 36 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:530860 HCAPLUS
DOCUMENT NUMBER: 127:232674
TITLE: Reduced expression of cyclin-dependent kinase inhibitor p27Kip1 is associated with advanced stage and invasiveness of gastric carcinomas
AUTHOR(S): Yasui, Wataru; Kudo, Yasusei; Semba, Shuho; Yokozaki, Hiroshi; Tahara, Eiichi
CORPORATE SOURCE: First Department of Pathology, Hiroshima University School of Medicine, Hiroshima, 734, Japan
SOURCE: Jpn. J. Cancer Res. (1997), 88(7), 625-629
CODEN: JJCREP; ISSN: 0910-5050
PUBLISHER: Japanese Cancer Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reduced expression of the cyclin-dependent kinase inhibitor p27Kip1 may predict poor survival of patients with breast and colorectal cancers. We studied the expression of p27Kip1 in gastric carcinomas by Northern blotting, Western blotting, and immunohistochem. to det. whether the lack of p27 has implications for aggressiveness of gastric cancer. Reduced expression of p27 was detected in 40% of the gastric carcinomas at the mRNA level, while it was detected in 57% at the protein level. No gross alterations of the p27 gene were obsd. in any of the cases examd. by Southern blot anal. Immunohistochem. studies revealed that the expression of p27 was well preserved in most of the gastric adenomas, whereas it was so in only 26% of the gastric carcinomas. In 56% of the carcinomas there were almost no p27-pos. cells. Decrease of p27-pos. cells significantly correlated with advanced stage, depth of tumor invasion, and lymph node **metastasis**. The expression of p27 showed an inverse correlation with the expression of cyclin E. These findings suggest that the redn. of p27Kip1 protein may reflect the progression of gastric carcinomas and may be an indicator of high-grade malignancy.

L10 ANSWER 37 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:661935 HCAPLUS
DOCUMENT NUMBER: 125:292489
TITLE: Impact of the cyclin-dependent kinase inhibitor p27Kip1 on resistance of tumor cells to anticancer agents
AUTHOR(S): Croix, Brad St.; Florenes, Vivi Ann; Rak, Janusz W.; Flanagan, Mike; Bhattacharya, Nandita; Slingerland,

Joyce M.; Kerbel, Robert S.
CORPORATE SOURCE: Division of Cancer Biology Res., Sunnybrook Health Science Center, Toronto, ON, M4N 3M5, Can.
SOURCE: Nat. Med. (N. Y.) (1996), 2(11), 1204-1210
CODEN: NAMEFI; ISSN: 1078-8956
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A low **proliferating** fraction in solid tumors limits the effectiveness of cell cycle-dependent chemotherapeutic agents. To understand the mol. basis of such "kinetic" resistance we cultured tumor cells as multicellular spheroids and examd. levels of p27Kip1, a cyclin-dependent kinase inhibitor known to be upregulated by intercellular contact in normal cells. When transferred from monolayer to three-dimensional culture, a consistent upregulation (up to 15-fold) of p27 protein was obsd. in a panel of mouse and human carcinoma cell lines. Antisense-oligonucleotide-mediated downregulation of p27 in EMT-6 mammary **tumor cell** spheroids reduced intercellular adhesion, increased cell **proliferation**, sensitized tumor cells to 4-hydroperoxycyclophosphamide, and restored drug- or radiation-induced cell-cycle perturbations repressed in spheroid culture. Our results implicate p27 as a regulator of drug resistance in solid tumors and suggest that tumor-targeted p27 antagonists may be useful chemosensitizers in conjunction with conventional anticancer therapy.

L10 ANSWER 38 OF 38 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:381173 HCAPLUS
DOCUMENT NUMBER: 125:55023
TITLE: The Epstein-Barr virus bZIP transcription factor Zta causes G0/G1 cell cycle arrest through induction of cyclin-dependent kinase inhibitors
AUTHOR(S): Cayrol, c.; Flemington, E. K.
CORPORATE SOURCE: Division tumor Virology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: EMBO J. (1996), 15(11), 2748-2759
CODEN: EMJODG; ISSN: 0261-4189
DOCUMENT TYPE: Journal
LANGUAGE: English
AB While oncoproteins encoded by small DNA tumor viruses and Epstein-Barr virus (EBV) latent antigens facilitate G1/S progression, the EBV lytic switch transactivator Zta was found to inhibit growth by causing cell cycle arrest in G0/G1 in several epithelial **tumor cell** lines. Expression of Zta results in induction of the tumor suppressor protein, p53, and the **cyclin-dependent kinase** inhibitors, p21 and **p27**, as well as accumulation of hypophosphorylated pRb. Up-regulation of p53 and p27 occurs by post-transcriptional mechanisms while expression of p21 is induced at the RNA level in a p53-dependent manner. Inactivation of pRb by transient overexpression of the human papillomavirus E7 oncoprotein indicates that pRb or pRb-related proteins are key mediators of the growth-inhibitory function of Zta. These findings suggest that EBV plays an active role in redirecting epithelial cell physiol. to facilitate the viral replicative program through a Zta-mediated growth arrest function.

=> d his full l23-l27

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:35:28 ON 24 MAY 2002)
L23 46 SEA L4(L)((METASTAS? OR METASTAT?)(5A)(NEOPLAS? OR CANCER? OR CARCIN? OR TUMOUR OR TUMOR))

```
L24          86 SEA (L4(L)(SMC OR (SMOOTH MUSCLE OR TUMOUR OR TUMOUR(W)
                CELL))(L)(PROLIFERAT? OR MIGRAT?))
L25           8 SEA (L4(L)((TREAT? OR THERAP?)(5A)(ATHEROSCLER? OR ARTERIOSCLER
                ? OR ARTERIOPATH? OR RESTENOSIS) OR (CARDIOVASCULAR OR CARDIO
                VASCULAR OR CARDIAC OR HEART)(5A)(DISORDER OR DISEAS?)))
L26         138 SEA L23 OR L24 OR L25
L27          62 DUP REMOVE L26 (76 DUPLICATES REMOVED)


=> d l27 ibib abs 1-62

L27  ANSWER 1 OF 62  WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER:     2002-255941 [30]   WPIDS
DOC. NO. CPI:         C2002-076291
TITLE:                New isolated and/or recombinant ubiquitin ligase such as
                      SIP (SKP Interacting Protein) ligase, for treating
                      diseases associated with aberrant protein degradation,
                      cell proliferation, differentiation, and cell survival.
DERWENT CLASS:        B04 D16
INVENTOR(S):          CALIGIURI, M; ROLFE, M
PATENT ASSIGNEE(S):   (CALI-I) CALIGIURI M; (ROLF-I) ROLFE M
COUNTRY COUNT:        1
PATENT INFORMATION:

     PATENT NO   KIND DATE     WEEK      LA   PG
     ----------------------------------------
     US 2002025569 A1 20020228 (200230)*      44

APPLICATION DETAILS:

     PATENT NO   KIND                  APPLICATION      DATE
     ------------------------------------------------------
     US 2002025569 A1                  US 1997-915048   19970820


PRIORITY APPLN. INFO: US 1997-915048   19970820
AN   2002-255941 [30]   WPIDS
AB   US2002025569 A UPAB: 20020513
     NOVELTY - An isolated and/or recombinant ubiquitin ligase (I), such as SIP
     (SKP Interacting Protein) ligase, for example isolated and/or recombinant
     cdc4 polypeptide comprising a sequence identical or homologous to a
     sequence (S1) comprising 1121 or 162 amino acids, given in the
     specification, is new.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
     following:
          (1) an isolated nucleic acid (II) comprising a sequence encoding a
     cdc4 polypeptide or its portion, or a complement or (II);
          (2) an isolated nucleic acid (III) comprising a sequence encoding a
     vertebrate SIP polypeptide;
          (3) an expression vector (IV) capable of replicating in a prokaryotic
     or eukaryotic cell comprising (IV);
          (4) a host cell (V) transfected with (IV) and expressing (I);
          (5) production of (I);
          (6) a transgenic animal (VI) having cells which harbor a transgene
     comprising (II) or (III), or in which a gene comprising (II) or (III) is
     disrupted;
          (7) an isolated nucleic acid (VII) which selectively hybridizes under
     high stringency conditions to at least 10 nucleotides of a sequence (S2)
     comprising 3363 or 484 base pairs, given in the specification, or its
     complement, where (VII) can specifically detect or amplify a sequence of a
```

vertebrate cdc4 gene;

(8) a reconstituted protein mixture (VIII) comprising an SIP polypeptide and a cell-cycle regulatory protein;

(9) an isolated SIP polypeptide (IX) having a ubiquitin group attached to cysteine;

(10) an assay (M1) for identifying an inhibitor of an SIP-mediated ubiquitination;

(11) an assay (M2) for identifying an inhibitor of an interaction between a substrate polypeptide and a SIP protein;

(12) diagnosing (M3) a hyperproliferative disorder in a patient where the disorder is associated with the destabilization of a CKI protein in cells of the patient, by ascertaining the level of expression of a SIP ligase in a sample of cells from the patient, and diagnosing the presence or absence of hyperproliferative disorder utilizing, at least in part, the ascertained level expression or activity of the ligase, where an increase level of a SIP protein or SIP ligase activity in the sample, relative to a normal control sample of cells, correlates with the presence of a hyperproliferative disorder; and

(13) a prognostic method (M4) for evaluating the aggressiveness and/or rate of recurrence of a disorder marked by aberrant hyperproliferation, aberrant dedifferentiation and/or aberrant apoptosis of cells, by ascertaining the level of SIP ligase expression and/or SIP ligase activity in a sample of cells from a patient, and ascertaining the aggressiveness and/or risk for recurrence of the disorder, at enzymatic activity, where an increased level in the sample, relative to a normal control sample of cells, correlates with a more aggressive form of the disorder and an increased risk of recurrence of the disorder.

ACTIVITY - Cytostatic; antipsoriatic; antiarteriosclerotic; antiinflammatory.

MECHANISM OF ACTION - Cell **proliferation**, differentiation, and/or survival modulator; cell-cycle of an eukaryotic cell regulator; entry of a mammalian or yeast cell into S phase modulator; wild-type form of SIP protein agonist/antagonist; gene therapy; antisense therapy. No biological data is given.

USE - (I) is useful for modulating cell **proliferation**, differentiation, and/or survival, and for treating diseases or conditions associated with aberrant protein degradation, cell **proliferation** , differentiation and/or cell survival, where the diseases are selected from cancer, leukemia, psoriasis, bone diseases, **proliferative** disorders such as involving connective tissues, atherosclerosis, and other **smooth muscle proliferative** disorder, and chronic inflammation. (I) is useful for mediating and/or catalyzing the transfer of a ubiquitin molecule from a relevant ubiquitin conjugating enzyme (UBC) to a lysine residue of its substrate protein, for regulating the cell-cycle of an eukaryotic cell, for modulating **proliferation** /cell growth of a eukaryotic cell, for modulating entry of a mammalian or yeast cell into S phase, for ubiquitination of a cell-cycle regulator, e.g., a **cyclin dependent kinase** inhibitor, e.g., **p27**, for modulating differentiation of cells/tissue, for modulating cell growth or **proliferation** by influencing the action of other cellular proteins, as a specific agonist of the function of the wild-type form of the protein, or as a specific antagonist, such as a catalytically inactive mutant. (I) is useful for generating an interaction trap assay and subsequently detecting agents with disrupt binding of the proteins. A nucleic acid (II) encoding (I) is useful for generating expression constructs and in antisense therapy.
Dwg.0/2

L27 ANSWER 2 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002159412 EMBASE

TITLE: High expression levels of p27 correlate with lymph node status in a subset of advanced invasive breast carcinomas: Relation to E-cadherin alterations, proliferative activity, and ploidy of the tumors.
AUTHOR: Kouvaraki M.; Gorgoulis V.G.; Rassidakis G.Z.; Liodis P.; Markopoulos C.; Gogas J.; Kittas C.
CORPORATE SOURCE: Dr. V.G. Gorgoulis, Antaiou 53 Street, Ano Patisia, Athens GR-11146, Greece. histoclub@ath.forthnet.gr
SOURCE: Cancer, (1 May 2002) 94/9 (2454-2465).
Refs: 76
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English

AB BACKGROUND. The **cyclin-dependent kinase** inhibitor **p27** plays a central role in cell cycle progression and is deregulated in breast carcinomas. Although its levels are inversely associated with tumor proliferation, overexpression of p27 has been reported in a subset of rapidly proliferating breast carcinoma cell lines. METHODS. p27 levels were determined by immunohistochemistry in a series of 52 sporadic invasive breast carcinomas consisting of 47 ductal, 2 lobular, and 3 mixed; most tumors were Grade 2 or 3 (46 of 52) and **Tumor** Node **Metastasis** (TNM) Stage II-IV (46 of 52). E-cadherin expression and its gene alterations at 16q22.1 were also studied, because in vitro evidence suggests a biologic association between p27 and E-cadherin-mediated growth suppression. RESULTS. The mean p27 labeling index (LI; percentage of p27 positive tumor cells) was 33.3% .+-. 25.3% (range, 0.1-85%). High p27 levels (p27 LI, > 50%) were observed in 14 (26.9%) of 52 **carcinomas** and were significantly associated with **metastatic** disease in axillary lymph nodes (14 of 33 vs. 0 of 19; P = 0.0007 by Fisher exact test). In addition, p27 LI was higher in the group of lymph node positive vs. lymph node negative tumors (mean p27 LI, 40.9% vs. 20.1%; P = 0.008 by Mann-Whitney test). Reduced or absent E-cadherin expression was found in 27 of 45 (60%) informative cases. Allelic imbalance of the 16q22.1 locus was found in 14 (27.5%) of 51 cases by using the microsatellite markers D16S503, D16S752, and D16S512. p27 LI and E-cadherin alterations were not statistically related. CONCLUSIONS. In summary, high p27 levels detected in a subset of advanced breast **carcinomas** correlate with lymph node **metastasis**, suggesting that other mechanisms may bypass the cell cycle inhibitory role of p27 and provide growth advantage in these tumors. .COPYRGT. 2002 American Cancer Society.

L27 ANSWER 3 OF 62 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002200347 MEDLINE
DOCUMENT NUMBER: 21849932 PubMed ID: 11861043
TITLE: Ovarian hormones induce TGF-beta(3) and fibronectin mRNAs but exhibit a disparate action on cardiac fibroblast proliferation.
AUTHOR: Mercier Isabelle; Colombo Federico; Mader Sylvie; Calderone Angelino
CORPORATE SOURCE: Departement de Physiologie, Universite de Montreal, Montreal, Quebec, Canada.
SOURCE: CARDIOVASCULAR RESEARCH, (2002 Feb 15) 53 (3) 728-39. Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020406
Last Updated on STN: 20020430
Entered Medline: 20020429

AB Prior to menopause, women have a lower risk of **cardiovascular disease** compared to age-matched men. Despite the well-documented beneficial physiological effects of ovarian hormones on vascular reactivity and growth, very little is known with regard to the direct action on cardiac cells. OBJECTIVE: The following study examined the pattern of ovarian hormone receptor subtype expression in cardiac fibroblasts, the modulator role of 17 beta-estradiol and progesterone on growth and their respective influence on putative molecular events of extracellular matrix remodeling. METHODS AND RESULTS: Neonatal rat cardiac fibroblasts were isolated from 1- to 3-day-old Sprague--Dawley rats. Immunofluorescence and Western blot analysis revealed the presence of estrogen receptor-alpha (ER-alpha), and -beta (ER-beta) subtypes, with the ER-alpha subtype localized on the plasma membrane. Likewise, both progesterone receptor-A (PR-A), and -B (PR-B) subtypes were expressed in cardiac fibroblasts, and the PR-B appeared to be the predominant subtype associated with the plasma membrane. Despite the presence of both ER subtypes, the treatment of cardiac fibroblasts with 1 microM 17 beta-estradiol exerted a modest decrease in DNA synthesis. By contrast, progesterone treatment caused a dose-dependent decrease in [3H]thymidine uptake, without a concomitant induction of apoptosis. The progesterone-mediated decrease in DNA synthesis was associated with the upregulation of the **cyclin-dependent kinase** inhibitor **p27**(Kip1), whereas p21(cip) and proliferating cell nuclear antigen protein levels were unchanged. Lastly, despite the modest effect on DNA synthesis, 17 beta-estradiol increased the steady-state mRNA levels of transforming growth factor-beta(3) and fibronectin. Likewise, progesterone increased the expression of both transforming growth factor-beta(3), and fibronectin mRNA. CONCLUSION: Collectively, these data are the first to highlight the presence of estrogen and progesterone receptor subtypes on the plasma membrane of neonatal rat cardiac fibroblasts, and further underscore the ability of ovarian hormones to directly suppress DNA synthesis, and influence putative molecular events associated with extracellular matrix remodeling.

L27 ANSWER 4 OF 62 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001697898 IN-PROCESS
DOCUMENT NUMBER: 21610276 PubMed ID: 11744034
TITLE: Mechanisms underlying maintenance of smooth muscle cell quiescence in rat aorta: role of the cyclin dependent kinases and their inhibitors.
AUTHOR: Izzard Tanya D; Taylor Christine; Birkett Sonia D; Jackson Christopher L; Newby Andrew C
CORPORATE SOURCE: Bristol Heart Institute, Bristol Royal Infirmary, BS2 8HW, Bristol, UK.
SOURCE: CARDIOVASCULAR RESEARCH, (2002 Jan) 53 (1) 242-52.
Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011218
Last Updated on STN: 20020123

AB Objective: We sought to understand why **smooth muscle**

cell **proliferation** is effectively repressed in intact rat aortic tissue. Methods: Quiescent isolated rat aortic **smooth muscle** cells and segments of intact rat aorta were stimulated with 10% serum and the time course of expression and activity of proteins involved in cell cycle control were determined. Results: After serum stimulation, **smooth muscle** cells in intact aortic tissue exhibit no **proliferation**, whereas isolated cells entered S phase 14-16 h later. Activation of ERKs 1 and 2, and induction of cyclin D1 occurred both in isolated cells and aortic tissue. Regulation of Cdk4, cyclin E and Cdk2 protein levels was also not different. Levels of the **cyclin-dependent kinase** inhibitors (CKIs), p16 and **p27**, were initially high in quiescent isolated cells and tissue; levels were downregulated by serum in isolated cells but not in aortic tissue. Cyclin D1/Cdk4, and cyclin E/Cdk2 kinases were active before S phase entry in isolated cells, but remained inactive in aortic tissue. Conclusions: Cell cycle entry is prevented in aortic tissue, and this is associated with an inability to downregulate p16 and p27 CKIs, and therefore to activate cyclin D1 and cyclin E associated kinase activities.

L27 ANSWER 5 OF 62 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002062611 MEDLINE
DOCUMENT NUMBER: 21648244 PubMed ID: 11788465
TITLE: Effects of dominant-negative c-Jun on platelet-derived growth factor-induced vascular smooth muscle cell proliferation.
AUTHOR: Zhan Yumei; Kim Shokei; Yasumoto Hideo; Namba Masashi; Miyazaki Hitoshi; Iwao Hiroshi
CORPORATE SOURCE: Department of Pharmacology, Osaka City University Medical School, Osaka, Japan.
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (2002 Jan) 22 (1) 82-8.
Journal code: 9505803. ISSN: 1524-4636.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020208
Entered Medline: 20020207

AB Although platelet-derived growth factor (PDGF)-BB is thought to participate in vascular disorders, the mechanism of PDGF-induced vascular **smooth muscle** cell (**SMC**) **proliferation** is not fully understood. This study was undertaken to examine the role of c-Jun in PDGF-BB-induced **proliferation** of rat aortic SMCs. PDGF-BB (10 ng/mL) significantly increased activator protein (AP)-1 DNA binding activity in SMCs, followed by the increase in [(3)H]thymidine incorporation and cell number. SMCs were infected with recombinant adenovirus containing TAM67, a dominant-negative c-Jun lacking the transactivation domain of wild c-Jun (Ad-DN-c-Jun), to inhibit endogenous AP-1. Ad-DN-c-Jun, which specifically blocked AP-1 transcriptional activity, significantly inhibited PDGF-BB-induced increases in [(3)H]thymidine incorporation or cell number. As shown by flow cytometric analysis, Ad-DN-c-Jun inhibited PDGF-BB-induced entrance of SMCs into S phase, leading to a G(1) arrest. Ad-DN-c-Jun attenuated PDGF-BB-induced downregulation of p27(Kip1), as shown by Western blot analysis, and the prevented PDGF-BB-induced decrease in cyclin E/**cyclin-dependent kinase** 2 complex-associated **p27** (Kip1), as shown by immunoprecipitation study. Furthermore, protein kinase assay showed that Ad-DN-c-Jun blocked PDGF-BB-induced activation of

cyclin-dependent kinase 2. Our results provide the first evidence that dominant-negative c-Jun inhibits PDGF-BB-induced vascular **SMC proliferation** by preventing the downregulation of p27(Kip1), thereby supporting the important role of c-Jun in vascular **SMC proliferation**.

L27 ANSWER 6 OF 62 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001349617 MEDLINE
DOCUMENT NUMBER: 21305844 PubMed ID: 11413088
TITLE: Role for p27(Kip1) in Vascular Smooth Muscle Cell Migration.
COMMENT: Comment in: Circulation. 2001 Jun 19;103(24):2879-81
AUTHOR: Sun J; Marx S O; Chen H J; Poon M; Marks A R; Rabbani L E
CORPORATE SOURCE: Cardiology Division, Center for Molecular Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: R03-TW-00949 (FIC)
RO1-AI-39794 (NIAID)
RO1-HL-30290 (NHLBI)
RO1-HL-56180 (NHLBI)
SOURCE: CIRCULATION, (2001 Jun 19) 103 (24) 2967-72.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB BACKGROUND: Rapamycin is a potent inhibitor of **smooth muscle** cell (**SMC**) **proliferation** and **migration**. Rapamycin-mediated inhibition of **SMC proliferation** is associated with upregulation of the **cyclin-dependent kinase** inhibitor **p27** (Kip1). Previously, we showed that mixed embryonic fibroblasts obtained from p27(Kip1)(-/-) mice were relatively rapamycin-resistant, suggesting that p27(Kip1) plays an integral role in modulating the antiproliferative effects of rapamycin. We hypothesized that the antimigratory effect of rapamycin may also be mediated by p27(Kip1). METHODS AND RESULTS: Rapamycin (1 to 10 nmol/L) inhibited basic fibroblast growth factor-induced **migration** of wild-type (WT) but not p27(Kip1)(-/-) SMCs in a dose-dependent manner ($P<0.05$) in a modified Boyden chamber. The effects of rapamycin on aortic **SMC** explant **migration** were also studied with WT, p27(+/-), and p27(-/-) mice. Rapamycin 4 mg. kg(-1). d(-1) IP for 5 days inhibited **SMC migration** by 90% in the WT and p27(Kip1)(+/-) ($P<0.05$) but not p27(Kip1)(-/-) animals. CONCLUSIONS: Lack of p27(Kip1) reduces rapamycin-mediated inhibition of **SMC migration**. These novel findings suggest a role for p27(Kip1) in the signaling pathway(s) that regulates **SMC migration**.

L27 ANSWER 7 OF 62 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001236577 MEDLINE
DOCUMENT NUMBER: 21214573 PubMed ID: 11313917
TITLE: Repression of transcription of the p27(Kip1) cyclin-dependent kinase inhibitor gene by c-Myc.
AUTHOR: Yang W; Shen J; Wu M; Arsura M; FitzGerald M; Suldan Z; Kim D W; Hofmann C S; Pianetti S; Romieu-Mourez R; Freedman L

P; Sonenshein G E
CORPORATE SOURCE: Department of Biochemistry, Boston University Medical School, Boston, Maryland, MA 02118, USA.
CONTRACT NUMBER: CA 36355 (NCI)
CA 82742 (NCI)
CA64070 (NCI)
HL07429 (NHLBI)
SOURCE: ONCOGENE, (2001 Mar 29) 20 (14) 1688-702.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB Upon engagement of the B Cell Receptor (BCR) of WEHI 231 immature B cells, a drop in c-Myc expression is followed by activation of the **cyclin -dependent kinase** inhibitor (CKI) **p27**(Kip1), which induces growth arrest and apoptosis. Here, we report inverse patterns of p27 and c-Myc protein expression follow BCR engagement. We present evidence demonstrating, for the first time, that the p27(Kip1) gene is a target of transcriptional repression by c-Myc. Specifically, the changes in p27 protein levels correlated with changes in p27 mRNA levels, and gene transcription. Induction of p27 promoter activity followed BCR engagement of WEHI 231 cells, and this induction could be repressed upon co-transfection of a c-Myc expression vector. Inhibition of the TATA-less p27 promoter by c-Myc was also observed in Jurkat T cells, vascular **smooth muscle**, and Hs578T breast cancer cells, extending the observation beyond immune cells. Consistent with a putative Inr element CCAGACC (where +1 is underlined) at the start site of transcription in the p27 promoter, deletion of Myc homology box II reduced the extent of repression. Furthermore, enhanced repression was observed upon transfection of the c-Myc 'super-repressor', with mutation of Phe115 to Leu. The sequences mediating transcriptional activity and c-Myc repression were mapped to bp -20 to +20 of the p27 gene. Finally, binding of Max was shown to facilitate c-Myc binding and repression of p27 promoter activity. Overall, these studies identify the p27 CKI gene as a new target whereby c-Myc can control cell **proliferation**, survival and neoplastic transformation.

L27 ANSWER 8 OF 62 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001551832 MEDLINE
DOCUMENT NUMBER: 21482516 PubMed ID: 11598171
TITLE: Prognostic significance of p27 and Ki-67 expression in mucoepidermoid carcinoma of the intraoral minor salivary gland.
AUTHOR: Okabe M; Inagaki H; Murase T; Inoue M; Nagai N; Eimoto T
CORPORATE SOURCE: Department of Pathology, Nagoya City University Medical School, Nagoya, Japan.
SOURCE: MODERN PATHOLOGY, (2001 Oct) 14 (10) 1008-14.
Journal code: 8806605. ISSN: 0893-3952.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011015
Last Updated on STN: 20020122

Entered Medline: 20011204

AB **p27** and Ki-67, a universal **cyclin-dependent kinase** inhibitor and a proliferative cell marker, respectively, have been useful in predicting clinical aggressiveness in various human tumors. We studied clinicopathologic significance of these molecules in mucoepidermoid carcinoma of the intraoral minor salivary gland. Expression of p27 and Ki-67 was assessed immunohistochemically in primary mucoepidermoid **carcinomas** from 31 patients without distant **metastasis** at surgery. Correlation each of p27 and Ki-67 expression was analyzed with various clinicopathologic parameters including age, sex, primary **tumor** site, **tumor** size, nodal **metastasis**, clinical stage, and histologic grade. The latter was evaluated using a point-scoring scheme of Auclair et al. that consists of five histologic factors (intracystic component, neural invasion, necrosis, mitosis, and anaplasia). p27 expression was correlated inversely with histologic grade (P =.007), but with none of other factors. When the correlation of p27 expression was further examined with each of the histologic factors, it was correlated significantly with intracystic component, but not with neural invasion, necrosis, mitosis, or anaplasia. Ki-67 expression was correlated significantly with histologic grade only in the clinicopathologic factors (P <.0001), and in the histologic factors, with necrosis, mitosis, and anaplasia. Multivariate prognostic analyses were performed to identify independent risk factors for both disease-free and overall survivals. Large tumor size (P =.031, relative risk = 5.5) and low p27 expression (P =.012, relative risk = 5.2) were risk factors for worse disease-free survival. Low p27 expression (P =.015, relative risk = 15.2) was selected as a risk factor for worse overall survival. Other factors including age, sex, tumor site, nodal status, clinical stage, histologic grade, and Ki-67 did not emerge as independent risk factors in either prognostic analysis. These data suggest that p27 may be useful in estimating prognosis of the patients who have mucoepidermoid carcinoma of the intraoral minor salivary gland.

L27 ANSWER 9 OF 62 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2001351352 MEDLINE
DOCUMENT NUMBER: 21299619 PubMed ID: 11406650
TITLE: Effect of p27 deficiency and rapamycin on intimal hyperplasia: in vivo and in vitro studies using a p27 knockout mouse model.
AUTHOR: Roque M; Reis E D; Cordon-Cardo C; Taubman M B; Fallon J T; Fuster V; Badimon J J
CORPORATE SOURCE: Cardiovascular Biology Research Laboratories, Mount Sinai School of Medicine, New York City, New York 10029-6574, USA.
SOURCE: LABORATORY INVESTIGATION, (2001 Jun) 81 (6) 895-903. Journal code: KZ4; 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB SUMMARY: Rapamycin, an immunosuppressant and antiproliferative agent, reduces intimal hyperplasia after arterial injury in animal models and in a preliminary study in humans. Rapamycin treatment reportedly increases expression of **p27**, a **cyclin-dependent kinase** inhibitor. This mechanism was tested using a p27-deficient (p27 -/-) murine model. Aortic **smooth muscle** cells

from wild-type (WT) and p27 -/- mice were isolated and cultured. Cell **proliferation**, assessed by cell count and (3)H-thymidine incorporation, was inhibited significantly by rapamycin in WT and p27 -/- cells at concentrations of 1 ng/ml, 10 ng/ml, and 100 ng/ml ($p < 0.05$, versus control). The in vivo effect on intimal hyperplasia was studied in p27 -/- and WT mice after femoral artery transluminal injury. Rapamycin treatment was started 2 days before injury and maintained for 2 weeks (1 mg/kg per 48 hours, ip). No significant differences in intima-to-media ratio were found between WT (1.1 +/- 0.1) and p27 -/- mice (1.0 +/- 0.1) 4 weeks after injury. Rapamycin significantly ($p < 0.05$) reduced intima-to-media ratios in both WT (0.7 +/- 0.1) and p27 -/- mice (0.5 +/- 0.1), compared with untreated mice. p27 deficiency did not alter the arterial wall **proliferative** response to injury. The inhibitory effect of rapamycin on intimal hyperplasia occurred via a p27-independent mechanism. The in vitro data showed that this effect was mediated through decreased **proliferation** and enhanced apoptosis.

L27 ANSWER 10 OF 62 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2001290523 MEDLINE
DOCUMENT NUMBER: 21267500 PubMed ID: 11348874
TITLE: Retroviral overexpression of decorin differentially affects the response of arterial smooth muscle cells to growth factors.
AUTHOR: Fischer J W; Kinsella M G; Levkau B; Clowes A W; Wight T N
CORPORATE SOURCE: Department of Pharmacology, Christian Albrechts University, Kiel, Germany.
CONTRACT NUMBER: HL-18645 (NHLBI)
HL-52459 (NHLBI)
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (2001 May) 21 (5) 777-84.
Journal code: B89; 9505803. ISSN: 1524-4636.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

AB Decorin is a member of the family of small leucine-rich proteoglycans that are present in blood vessels and synthesized by arterial **smooth muscle** cells (ASMCs). This proteoglycan accumulates in topographically defined regions of atherosclerotic lesions and may play a role in the development of this disease. However, little is known about whether decorin has specific effects on the cellular events that contribute to atherosclerotic lesion formation. In the present study, rat ASMCs were transduced with a retroviral vector (LDSN) that carries the bovine decorin gene. Compared with vector control cells (LXSN), these cells constitutively overexpress decorin, as verified by Northern and Western analysis and by metabolic labeling. Experiments were performed to examine the responsiveness of decorin-overexpressing rat ASMCs to platelet-derived growth factor (PDGF) and transforming growth factor-beta1 (TGF-beta1), 2 growth factors that affect cell **proliferation** and extracellular matrix production in atherosclerosis. Decorin-overexpressing cells had decreased [(3)H]thymidine incorporation into DNA and increased the levels of the **cyclin-dependent kinase** inhibitors p21 and **p27** in the first 24 hours of response to serum and PDGF-BB. However, these effects of decorin were not apparent at 48 or 72 hours after plating and did not result in reduced growth of decorin-overexpressing cells in response to serum and PDGF-BB. In

contrast, the growth response of decorin-overexpressing ASMCs to TGF-beta1, as well as the expression of TGF-beta1-responsive genes, such as plasminogen activator inhibitor-1 and versican (an extracellular matrix proteoglycan), was diminished. These results indicate that decorin selectively inhibits the responsiveness of rat ASMCs to TGF-beta1 and suggests that the induction of constitutive decorin overexpression by ASMCs in vivo may have therapeutic value in the inhibition of TGF-beta1-mediated effects on the development of atherosclerotic lesions.

L27 ANSWER 11 OF 62 MEDLINE
ACCESSION NUMBER: 2001700356 MEDLINE
DOCUMENT NUMBER: 21569748 PubMed ID: 11713109
TITLE: p27(Kip1) is important in modulating pulmonary artery smooth muscle cell proliferation.
AUTHOR: Fouty B W; Grimison B; Fagan K A; Le Cras T D; Harral J W; Hoedt-Miller M; Sclafani R A; Rodman D M
CORPORATE SOURCE: Center for Genetic Lung Disease and Division of Pulmonary Sciences and Critical Care Medicine, Department of Biochemistry, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.. brian.fouty@uchsc.edu
CONTRACT NUMBER: HL48038-09 (NHLBI)
P01 HL 14985-29 (NHLBI)
RO1 CA58187-085P50 (NCI)
RO1 HL57282-03 (NHLBI)
SOURCE: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (2001 Nov) 25 (5) 652-8.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011220
Last Updated on STN: 20020125
Entered Medline: 20020109

AB Vascular remodeling due to pulmonary arterial **smooth muscle** cell (PASMC) **proliferation** is central to the development of pulmonary hypertension. Cell **proliferation** requires the coordinated interaction of cyclins and cyclin-dependent kinases (cdk) to drive cells through the cell cycle. Cdk inhibitors can bind cyclin-cdk complexes and cause G(1) arrest. To determine the importance of the **cdk** inhibitor **p27**(Kip1) in PASMC **proliferation** we studied [(3)H]thymidine incorporation, changes in cell cycle, cell **proliferation**, and protein expression of p27(Kip1) following serum stimulation in early passage rat PASMC. p27(Kip1) expression decreased to 40% of baseline after serum stimulation, which was associated with an increase in both [(3)H]thymidine incorporation and the percent of cells in S phase. p27(Kip1) binding to cyclin E decreased at 24 h, and this correlated with an increase in phosphorylation of retinoblastoma both in vivo and in vitro. Overexpression of p27(Kip1) decreased [(3)H]thymidine incorporation and reduced cell counts at 5 d compared with controls. PASMC obtained from p27(Kip1-/-) mice showed a 2-fold increase in [(3)H]thymidine incorporation (at 24 h) and cell **proliferation** compared with p27(Kip1+/+) PASMC when cultured in 10% fetal bovine serum (FBS). These results suggest an important role for p27(Kip1) in regulating PASMC mitogenesis and **proliferation**.

L27 ANSWER 12 OF 62 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2002090866 MEDLINE

DOCUMENT NUMBER: 21600303 PubMed ID: 11738067
TITLE: Beraprost sodium regulates cell cycle in vascular smooth muscle cells through cAMP signaling by preventing down-regulation of p27(Kip1).
AUTHOR: Ii M; Hoshiga M; Fukui R; Negoro N; Nakakoji T; Nishiguchi F; Kohbayashi E; Ishihara T; Hanafusa T
CORPORATE SOURCE: First Department of Internal Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, 569-8686, Osaka, Japan.. in1041@poh.osaka-med.ac.jp
SOURCE: CARDIOVASCULAR RESEARCH, (2001 Dec) 52 (3) 500-8. Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020201
Last Updated on STN: 20020220
Entered Medline: 20020219

AB OBJECTIVE: Beraprost sodium (BPS), a prostacyclin (PGI(2)) analogue, has been reported to exhibit beneficial effects on atherosclerosis in both human and animal models. To clarify the underlying mechanism, we investigated the effects of BPS on neointimal formation after balloon injury in the canine coronary artery. Furthermore, we determined its anti-atherosclerotic effects in cultured **smooth muscle** cells (SMCs). METHODS: Adult beagle dogs (10-12 kg) were fed on a high-cholesterol diet (10 g/day) and underwent balloon-denudation of the coronary artery. The dogs were divided into two groups: a BPS-treated group (20 microg/kg per day) and a control group. Twenty-eight days after injury, the dogs were killed and the coronary arteries were examined morphometrically. Three days after injury, the **proliferative** activity in the medial layer of the coronary artery was evaluated by 5-bromo-2'-deoxyuridine (BrdU) incorporation, and **p27**(Kip1), a **cyclin-dependent kinase** (**cdk**) inhibitor, expression was examined by immunohistochemistry. We also examined the effects of BPS on **SMC proliferation** based on BrdU incorporation and cell cycle analysis. In addition, p27(Kip1) regulation was evaluated in primary-cultured SMCs. RESULTS: BPS administration decreased the intima/media ratio (I/M) by 88% in the control group. Three days after injury, BPS attenuated the **proliferation** rate of the cells in the media of the coronary artery by 35%, and maintained p27(Kip1) expression, which declined in the control cells. In the cultured **proliferating SMC**, BPS prevented the down-regulation of p27(Kip1). The 8-bromo-cyclic adenosine monophosphate (8-br-cAMP), a cAMP analogue, had similar actions as BPS in the regulation of p27(Kip1). The **proliferation** of cultured **SMC** was inhibited in a dose-dependent manner, and cell cycle arrest in the G1 phase was induced by BPS. CONCLUSIONS: Our data suggest that BPS inhibits neointimal formation after balloon denudation in the coronary artery through its inhibitory effect on **SMC proliferation** by preventing p27(Kip1) down-regulation.

L27 ANSWER 13 OF 62 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001509974 MEDLINE
DOCUMENT NUMBER: 21441487 PubMed ID: 11557735
TITLE: Increased expression and activity of RhoA are associated with increased DNA synthesis and reduced p27(Kip1) expression in the vasculature of hypertensive rats.
AUTHOR: Seasholtz T M; Zhang T; Morissette M R; Howes A L; Yang A H; Brown J H

CORPORATE SOURCE: University of California, San Diego, Department of Pharmacology, La Jolla, USA.
CONTRACT NUMBER: GM-07752 (NIGMS)
GM-36927 (NIGMS)
HL-28143 (NHLBI)
HL-35018 (NHLBI)
SOURCE: CIRCULATION RESEARCH, (2001 Sep 14) 89 (6) 488-95.
Journal code: DAJ; 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010917
Last Updated on STN: 20011015
Entered Medline: 20011011

AB We have previously shown that the function of the small G protein Rho is required for vascular **smooth muscle** cell **proliferation** and **migration**. We hypothesized that changes in Rho or Rho signaling might contribute to enhanced vascular **proliferative** responses associated with hypertension. Western blot analysis revealed that total RhoA expression was approximately 2-fold higher in aortas, tail arteries, and aortic **smooth muscle** cells (ASMCs) obtained from adult male spontaneously hypertensive rats (SHR) compared with those from Wistar Kyoto rats (WKY). An increase in active GTP-bound RhoA was detected in aortic homogenates by affinity precipitation with the RhoA effector rhotekin and by examining RhoA-[(35)S]GTPgammaS binding. RhoA protein and activity were also increased in vessels from rats treated with N-nitro-L-arginine methyl ester to increase blood pressure. Thrombin-stimulated RhoA activation was also significantly greater in ASMCs from SHR. As a functional correlate of these changes in Rho signaling, thrombin-stimulated DNA synthesis was enhanced in tail arteries and ASMCs from SHR. Expression of the **cyclin-dependent kinase** inhibitor **p27** (Kip1) was decreased by two thirds in SHR, and this decrease was mimicked in ASMCs by expression of a constitutively active (GTPase-deficient) mutant of RhoA. Wortmannin (10 nmol/L) fully inhibited the decrease in p27(Kip1) induced by RhoA, and a membrane-targeted catalytic subunit of phosphatidylinositol-3 kinase (PI3K [p110(CAAX)]) decreased p27(Kip1) expression, suggesting that RhoA signals through PI3K. These data provide evidence that RhoA brings about changes in DNA synthesis through reduced expression of p27(Kip1), mediated in part via PI3K, and suggest that increases in RhoA expression and activity contribute to the enhanced vascular responsiveness observed in hypertension.

L27 ANSWER 14 OF 62 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2001696618 MEDLINE
DOCUMENT NUMBER: 21611890 PubMed ID: 11745678
TITLE: The expression of Ki-67, MCM3, and p27 defines distinct subsets of proliferating, resting, and differentiated cells.
AUTHOR: Endl E; Kausch I; Baack M; Knippers R; Gerdes J; Scholzen T
CORPORATE SOURCE: Department of Immunology and Cell Biology, Division of Molecular Immunology, Research Center Borstel, D-23845 Borstel, Germany.. eendl@fz-borstel.de
SOURCE: JOURNAL OF PATHOLOGY, (2001 Nov) 195 (4) 457-62.
Journal code: 0204634. ISSN: 0022-3417.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20011218
Last Updated on STN: 20020205
Entered Medline: 20020204

AB The mini-chromosome maintenance proteins (MCM), which are involved in the control of DNA replication, and the **cyclin-dependent kinase** inhibitors, such as **p27**/KIP1, represent two groups of proteins that are currently under investigation as diagnostic **tumour** markers. The expression of p27 and MCM3 was compared with the expression of the Ki-67 protein, an approved marker for **proliferating** cells, extensively used in histopathology and cancer research. The expression pattern of all three proteins was assessed on germinal centres and oral mucosa, which display a well-defined spatio-temporal organization. The expression of the p27 protein was closely related to differentiated cells, whereas MCM3 and Ki-67 were predominantly localized to the regions of **proliferating** cells. However, it is important to note that considerable numbers of cells that were growth-arrested, as confirmed by the absence of the Ki-67 protein, stained positive for the MCM3 protein. These results were verified in vitro using growth-arrested Swiss 3T3. The MCM3 protein is therefore expressed in cells that have ceased to **proliferate**, but are not terminally differentiated, according to the absence of p27 protein expression. In conclusion, a combined analysis of Ki-67, MCM3, and p27 protein expression may provide a more detailed insight into the cell **proliferation** and differentiation processes that determine individual **tumour** growth.

L27 ANSWER 15 OF 62 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 2001695590 MEDLINE
DOCUMENT NUMBER: 21610808 PubMed ID: 11745414
TITLE: CDK-inhibitors-associated kinase activity: a possible determinant of malignant potential in smooth muscle tumors of the external soft tissue.
AUTHOR: Dobashi Y; Noguchi T; Nasuno S; Katayama K; Kameya T
CORPORATE SOURCE: Department of Pathology, Kitasato University School of Medicine, Kanagawa, Japan.. ydobashi@med.kitasato-u.ac.jp
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2001 Nov 1) 94 (3) 353-62.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011218
Last Updated on STN: 20020125
Entered Medline: 20020107

AB There has been accumulating histological observation of leiomyoma and leiomyosarcoma of the external soft tissue regarding their differential diagnosis. The definitive diagnostic tools have not been established, however, nor have the pathological mechanisms of cell **proliferation** in these tumors been clarified. Herein, expression of the **cyclin-dependent kinase** inhibitors (CKIs), p21, **p27** and p57 and their associated kinase activities were examined in 61 cases of soft tissue **smooth muscle** tumors. Immunohistochemical staining showed that all 3 inhibitor proteins were expressed in all cases of leiomyoma and leiomyosarcoma, but that the mean values of their labeling indices (LIs) were higher in the cases of

leiomyosarcoma. In addition, the LIs of p21 and p27 were inversely correlated in total cases. Immunoblotting revealed that these proteins are expressed at higher levels in tumors, in particular, in leiomyosarcoma. When CKIs were immunoprecipitated from tissue extracts, cyclin/cdk protein complexes associated with, at least, 1 CKI were detectable only in tumor tissues. Furthermore, cdk2 or cdk4 kinase activity manifested by these cyclin/cdk/CKI complexes (CKI-associated kinase activity) was detectable exclusively from leiomyosarcoma, but not from leiomyoma. Among the cases of leiomyosarcoma, cdk2 activity was generally found associated either with p21 or p27, but not both. Statistical analysis indicated that p21- and p27 LIs are predictive of positive or negative clinical outcome, respectively. In conclusion, the participation of CKIs in active cyclin/cdk complexes in a reciprocal and redundant manner and subsequent CKI- associated kinase activity are the characteristic profiles of malignant phenotype in these tumors. Moreover, immunohistochemical detection of CKIs may provide a useful tool for evaluating patients' prognosis.

L27 ANSWER 16 OF 62 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 2001532909 MEDLINE
DOCUMENT NUMBER: 21449049 PubMed ID: 11565035
TITLE: A mouse knock-in model exposes sequential proteolytic pathways that regulate p27Kip1 in G1 and S phase.
AUTHOR: Malek N P; Sundberg H; McGrew S; Nakayama K; Kyriakidis T R; Roberts J M
CORPORATE SOURCE: Howard Hughes Medical Institute, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104, USA.
SOURCE: NATURE, (2001 Sep 20) 413 (6853) 323-7.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011003
Last Updated on STN: 20011029
Entered Medline: 20011025

AB The protein p27Kip1 is an inhibitor of cell division. An increase in p27 causes **proliferating** cells to exit from the cell cycle, and a decrease in p27 is necessary for quiescent cells to resume division. Abnormally low amounts of p27 are associated with pathological states of excessive cell **proliferation**, especially cancers. In normal and **tumour** cells, p27 is regulated primarily at the level of translation and protein turnover. Phosphorylation of **p27** on threonine 187 (T187) by **cyclin-dependent kinase** 2 (Cdk2) is thought to initiate the major pathway for p27 proteolysis. To critically test the importance of this pathway in vivo, we replaced the murine p27 gene with one that encoded alanine instead of threonine at position 187 (p27T187A). Here we show that cells expressing p27T187A were unable to downregulate p27 during the S and G2 phases of the cell cycle, but that this had a surprisingly modest effect on cell **proliferation** both in vitro and in vivo. Our efforts to explain this unexpected result led to the discovery of a second proteolytic pathway for controlling p27, one that is activated by mitogens and degrades p27 exclusively during G1.

L27 ANSWER 17 OF 62 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 2001226348 MEDLINE
DOCUMENT NUMBER: 21113397 PubMed ID: 11179200

TITLE: Membrane-bound protein kinase A inhibits smooth muscle cell proliferation in vitro and in vivo by amplifying cAMP-protein kinase A signals.
AUTHOR: Indolfi C; Stabile E; Coppola C; Gallo A; Perrino C; Allevato G; Cavuto L; Torella D; Di Lorenzo E; Troncone G; Feliciello A; Avvedimento E; Chiariello M
CORPORATE SOURCE: Division of Cardiology, "Magna Graecia" University, Catanzaro, Italy.
SOURCE: CIRCULATION RESEARCH, (2001 Feb 16) 88 (3) 319-24. Journal code: DAJ; 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010521
Entered Medline: 20010426

AB cAMP-dependent protein kinase is anchored to discrete cellular compartments by a family of proteins, the A-kinase anchor proteins (AKAPs). We have investigated in vivo and in vitro the biological effects of the expression of a prototypic member of the family, AKAP75, on **smooth muscle** cells. In vitro expression of AKAP75 in **smooth muscle** cells stimulated cAMP-induced transcription, increased the levels of the **cyclin-dependent kinase**-2 inhibitor **p27**(kip1), and reduced cell **proliferation**. In vivo expression of exogenous AKAP75 in common carotid arteries, subjected to balloon injury, significantly increased the levels of p27(kip1) and inhibited neointimal hyperplasia. Both the effects in **smooth muscle** cells in vitro and in carotid arteries in vivo were specifically dependent on the amplification of cAMP-dependent protein kinase (PKA) signals by membrane-bound PKA, as indicated by selective loss of the AKAP75 biological effects in mutants defective in the PKA anchor domain or by suppression of AKAP effects by the PKA-specific protein kinase inhibitor. These data indicate that AKAP proteins selectively amplify cAMP-PKA signaling in vitro and in vivo and suggest a possible target for the inhibition of the neointimal hyperplasia after vascular injury.

L27 ANSWER 18 OF 62 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 2001493707 MEDLINE
DOCUMENT NUMBER: 21427671 PubMed ID: 11536304
TITLE: Methylation and mutational analysis of p27(kip1) in prostate carcinoma.
AUTHOR: Kibel A S; Christopher M; Faith D A; Bova G S; Goodfellow P J; Isaacs W B
CORPORATE SOURCE: Department of Surgery, Washington University School of Medicine, St. Louis, Missouri 63105, USA.. kibela@msnotes.wustl.edu
CONTRACT NUMBER: CA 58236 (NCI)
CA 59457 (NCI)
SOURCE: PROSTATE, (2001 Sep 15) 48 (4) 248-53. Journal code: PB4; 8101368. ISSN: 0270-4137.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20011008

Entered Medline: 20011004

AB BACKGROUND: We have previously identified 12p12-13 as a region of frequent genetic loss in prostate carcinoma. A candidate tumor suppressor gene at this locus is the **cyclin dependent kinase** inhibitor **p27**(kip1), which has been implicated as a marker of aggressive prostate **carcinoma**. Herein, we examine **metastatic** prostate tumors, xenografts, and cell lines for gene inactivation via mutational inactivation or promoter hypermethylation. METHODS: Mutation analysis was performed on metastatic prostate tumors of 18 patients, eight prostate carcinoma cell lines, and 18 xenografts by PCR amplification of the entire open reading frame of p27(kip1). PCR products were sequenced directly using internal primers. Methylation analysis was performed on four cell lines and nine xenografts using direct sequencing of cloned PCR products of bisulfite treated DNA. Presence of a CpG was consistent with methylation of that cytosine in the original sample. RESULTS: With the exception of the previously reported homozygous deletion, no additional mutations were identified. Methylated CpG residues were identified in three xenografts (LuCAP23, LuCAP35, and PC82) and the methylated residues clustered at six sites; the cytosines 69, 149, 191, 286, 349, and 487 base pairs 5' of the ATG start codon. However, no sample demonstrated promotor methylation in all sequenced clones and the number of methylated base pairs ranged from seven to three, not the level usually associated with gene silencing. CONCLUSIONS: Mutational inactivation of p27(kip1) is a rare event in **metastatic** prostate **carcinoma**. While CpG methylation does occur, it is an infrequent event and does not appear to be the mechanism of p27(kip1) down regulation in prostate carcinoma.

L27 ANSWER 19 OF 62 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 2001345413 MEDLINE
DOCUMENT NUMBER: 21301548 PubMed ID: 11408921
TITLE: Loss of p27 expression predicts poor prognosis in patients with Dukes' B stage or proximal colorectal cancer.
AUTHOR: Zhang H; Sun X F
CORPORATE SOURCE: Department of Dermatology, Institute of Biomedicine and Surgery, Linkoping University, S-581 85 Linkoping, Sweden.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2001 Jul) 19 (1) 49-52. Journal code: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010827
Entered Medline: 20010823

AB **p27** is a **cyclin-dependent kinase** inhibitor which regulates progression of cells from G1 into S phase in a cell cycle. Loss of the negative regulator may contribute to oncogenesis and tumor progression. The aim of this study was to examine p27 expression in normal mucosa, primary and metastatic tumors from patients with colorectal adenocarcinomas and to analyze association of p27 with patient survival and clinicopathological variables. p27 expression was estimated by immunohistochemistry in 178 primary colorectal **cancers**, 34 lymph node **metastases** and 48 normal mucosa samples from patients with colorectal adenocarcinoma. Associations of p27 with patient survival, clinicopathological characteristics and expression of p53, p73 and DCC were analyzed. Loss of p27 was found in 51% of primary tumors, 68% of metastases and 56% of normal samples. The intensity of p27 staining was

similar in the matched primary **tumor**, **metastasis** and normal mucosa. In patients with Dukes' B or with proximal tumors, the loss of p27 predicted poorer prognosis ($p = 0.03$ and $p = 0.05$, respectively). However, there were no significant differences in the patients with other individual Dukes' stage or distal tumors. No relationships were found between p27 and patients' gender, age, tumor location, growth pattern and expression of p53, p73 and DCC ($p > 0.05$). The data suggest that loss of p27 was associated with poor prognosis in patients with Dukes' B tumor or those with proximal tumor. p27 might be a useful marker to identify the more progressive tumors in these groups.

L27 ANSWER 20 OF 62 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 2001174602 MEDLINE
DOCUMENT NUMBER: 21130631 PubMed ID: 11235905
TITLE: Deregulated expression of cell cycle-associated proteins in solid pseudopapillary tumor of the pancreas.
AUTHOR: Muller-Hocker J; Zietz C H; Sendelhofert A
CORPORATE SOURCE: Institute of Pathology, University of Munich, Germany.
SOURCE: MODERN PATHOLOGY, (2001 Feb) 14 (2) 47-53.
Journal code: PTH; 8806605. ISSN: 0893-3952.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Solid pseudopapillary tumor of the pancreas was studied in a 20-year-old woman and a 54-year-old woman. In the younger patient, the **tumor** had **metastasized** to the liver 8 years after distal pancreatectomy. In both neoplasms, the distinct histologic pattern of solid, pseudopapillary, and degenerative cystic areas was present. Analysis by means of immunohistochemistry revealed a diffuse expression for vimentin, neuron-specific enolase, and a focal positivity for al-antitrypsin, whereas epithelial markers were negative in the tumor of the older patient and only focally expressed in the tumor of the younger patient. Immunohistochemical analysis of cell cycle-associated proteins provided an overexpression of cyclin D1 and cyclin D3 in both tumors, although to varying degrees. In addition, the cyclin-dependent kinase inhibitors p21, and to a lesser extent p27, were up-regulated just as mdm2. There was no accumulation of p53 protein, and Ki67-positive cells were extremely scarce. Analysis of the liver metastases showed an immunoreactive profile similar to that of the primary tumor. The results show a deregulation of the cell cycle with overexpression of cell cycle-activating proteins D1 and D3 and a probably counterbalancing upregulation of the **cyclin-dependent kinase** inhibitors p21 and **p27**. The findings may explain the low pool of Ki67-reactive tumor cells and the generally good clinical outcome of these tumors. Whether a more profound dysbalance of the cell cycle regulation is responsible for the development of metastatic disease remains to be clarified.

L27 ANSWER 21 OF 62 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 2000388536 MEDLINE
DOCUMENT NUMBER: 20351602 PubMed ID: 10891505
TITLE: Evidence for a telomere-independent "clock" limiting RAS oncogene-driven proliferation of human thyroid epithelial cells.
AUTHOR: Jones C J; Kipling D; Morris M; Hepburn P; Skinner J;

Bounacer A; Wyllie F S; Ivan M; Bartek J; Wynford-Thomas D; Bond J A
CORPORATE SOURCE: Cancer Research Campaign Laboratories, Department of Pathology, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, United Kingdom.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Aug) 20 (15) 5690-9. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000810

AB An initiating role for RAS oncogene mutation in several epithelial cancers is supported by its high incidence in early-stage tumors and its ability to induce **proliferation** in the corresponding normal cells in vitro. Using retroviral transduction of thyroid epithelial cells as a model we ask here: (i) how mutant RAS can induce long-term **proliferation** in an epithelial cell in contrast to the premature senescence observed in fibroblasts; and (ii) what is the "clock" which eventually triggers spontaneous growth arrest even in epithelial clones generated by mutant RAS. The early response to RAS activation in thyroid epithelial cells showed two features not seen in fibroblasts: (i) a marked decrease in expression of the **cyclin-dependent kinase** inhibitor (CDKI) **p27**(kip1) and (ii) the absence of any induction of p21(waf1). When **proliferation** eventually ceased (after up to 20 population doublings) this occurred despite undiminished expression of mutant RAS and was tightly correlated with a return to the initial high level of p27(kip1) expression, together with the de novo appearance of p16(ink4a). Importantly, neither the CDKI changes nor the **proliferative** life span of RAS-induced epithelial clones was altered by induction of telomerase activity through forced expression of the catalytic subunit, hTERT, at levels sufficient to immortalize human fibroblasts. These data provide a basis for cell-type differences in sensitivity to RAS-induced **proliferation** which may explain the corresponding tumor-type specificity of RAS mutation. They also show for the first time in a primary human cell model that a telomere-independent mechanism can limit not only physiological but also oncogene-driven **proliferation**, pointing therefore to a **tumour** suppressor mechanism additional, or alternative, to the telomere clock.

L27 ANSWER 22 OF 62 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 2000502358 MEDLINE
DOCUMENT NUMBER: 20502864 PubMed ID: 11044431
TITLE: Inhibition of vascular smooth muscle cell proliferation by sodium salicylate mediated by upregulation of p21(Waf1) and p27(Kip1).
COMMENT: Comment in: Circulation. 2000 Oct 24;102(17):2022-3
AUTHOR: Marra D E; Simoncini T; Liao J K
CORPORATE SOURCE: Cardiovascular Division, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA.
CONTRACT NUMBER: HL-48743 (NHLBI)
HL-52233 (NHLBI)
SOURCE: CIRCULATION, (2000 Oct 24) 102 (17) 2124-30. Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010521
Entered Medline: 20001113

AB BACKGROUND: Salicylates may have direct vascular effects by mechanisms that are independent of platelet inhibition. METHODS AND RESULTS: We investigated the effect of salicylates on vascular **smooth muscle** cell (**SMC**) **proliferation** in response to platelet-derived growth factor (PDGF) in vitro. Salicylate concentrations of 5 and 10 mmol/L inhibited serum- or PDGF-induced **SMC** cell count and [(3)H]thymidine incorporation by 62% and 81%, respectively. There was no evidence of cellular toxicity or apoptosis as determined by trypan blue exclusion and FACS analyses. Because cell cycle progression is regulated by hyperphosphorylation of the retinoblastoma (Rb) protein, we examined the effects of salicylate on Rb hyperphosphorylation. Treatment with salicylate, but not indomethacin, inhibited nuclear factor-kappaB activation and completely abolished Rb hyperphosphorylation in PDGF-treated SMCs. This effect was associated with a decrease in cyclin-dependent kinase (Cdk)-2 and, to a lesser extent, Cdk-6, but not Cdk-4 activity, without changes in Cdk-2, -4, and -6 and cyclin D and E protein levels. Because Cdk-2 activity is regulated by the **Cdk** inhibitors p21(Waf1) and **p27**(Kip1), we studied the effects of salicylate on p21(Waf1) and p27(Kip1) expression. Treatment with salicylate prevented PDGF-induced downregulation of p21(Waf1) and **p27**(Kip1) but not of the **Cdk**-4/-6 inhibitor p16(Ink4). CONCLUSIONS: These findings indicate that high doses of salicylates inhibit **SMC proliferation** by cell cycle arrest at the G(1)-S phase and suggest a beneficial role for high-dose salicylates in the treatment of vascular **proliferative** disorders.

L27 ANSWER 23 OF 62 MEDLINE
ACCESSION NUMBER: 2000253779 MEDLINE
DOCUMENT NUMBER: 20253779 PubMed ID: 10790342
TITLE: Inhibition of rho-associated kinase results in suppression of neointimal formation of balloon-injured arteries.
AUTHOR: Sawada N; Itoh H; Ueyama K; Yamashita J; Doi K; Chun T H; Inoue M; Masatsugu K; Saito T; Fukunaga Y; Sakaguchi S; Arai H; Ohno N; Komeda M; Nakao K
CORPORATE SOURCE: Departments of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto, Japan.
SOURCE: CIRCULATION, (2000 May 2) 101 (17) 2030-3.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20020420
Entered Medline: 20000516

AB BACKGROUND: Rho-associated kinase (ROCK), an effector of small GTPase Rho, regulates vascular tone via a calcium sensitization mechanism and plays a key role in the pathogenesis of hypertension. However, its role in vascular growth remains unclear. METHODS AND RESULTS: Y-27632, a specific ROCK inhibitor, and the overexpression of dominant-negative ROCK suppressed the mitogen-induced DNA synthesis of cultured vascular **smooth muscle** cells (VSMCs), which indicates the essential role of ROCK in the control of VSMC **proliferation** in

vitro. Y-27632 also suppressed the chemotaxis of VSMCs. Male Wistar rats were systemically given Y-27632 (35 to 70 mg. kg(-1). day(-1)) through an intraperitoneal infusion. The neointimal formation of balloon-injured carotid arteries was significantly suppressed in Y-27632-treated rats (intima/media ratio, 0.22+/-0.02) compared with vehicle-treated rats (intima/media ratio, 0.92+/-0.21) or hydralazine-treated rats with a similar blood pressure decrease (intima/media ratio, 1.03+/-0.15). The phosphorylation of myosin phosphatase and myosin light chain was elevated in injured arteries in a Y-27632-sensitive manner, indicating the augmentation of ROCK activity in neointimal formation. The downregulation of the **cyclin-dependent kinase** inhibitor **p27**(kip1) in injured vessels was reversed by Y-27632 treatment, reflecting the antiproliferative effect of ROCK inhibition in vivo. CONCLUSIONS: We conclude that ROCK plays a key role in the process of neointimal formation after balloon injury. Thus, the inhibition of ROCK may be a potential therapeutic strategy for treating vascular **proliferative** disorders and hypertension.

L27 ANSWER 24 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000154573 EMBASE
TITLE: Inhibition of Rho-associated kinase results in suppression of neointimal formation of balloon-injured arteries.
AUTHOR: Naoki S.; Itoh H.; Ueyama K.; Yamashita J.; Doi K.; Chun T.-H.; Inoue M.; Masatsugu K.; Saito T.; Fukunaga Y.; Sakaguchi S.; Arai H.; Ohno N.; Komeda M.; Nakao K.
CORPORATE SOURCE: Dr. H. Itoh, Dept. of Med. and Clinical Science, Kyoto Univ. Graduate Sch. of Med., 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. hiito@kuhp.kyoto-u.ac.jp
SOURCE: Circulation, (2 May 2000) 101/17 (2030-2033).
Refs: 11
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background - Rho-associated kinase (ROCK), an effector of small GTPase Rho, regulates vascular tone via a calcium sensitization mechanism and plays a key role in the pathogenesis of hypertension. However, its role in vascular growth remains unclear. Methods and Results - Y-27632, a specific ROCK inhibitor, and the overexpression of dominant-negative ROCK suppressed the mitogen-induced DNA synthesis of cultured vascular **smooth muscle** cells (VSMCs), which indicates the essential role of ROCK in the control of VSMC **proliferation** in vitro. Y-27632 also suppressed the chemotaxis of VSMCs. Male Wistar rats were systemically given Y-27632 (35 to 70 mg .cntdot. kg-1 .cntdot. day-1) through an intraperitoneal infusion. The neointimal formation of balloon- injured carotid arteries was significantly suppressed in Y-27632-treated rats (intima/media ratio, 0.22.+-.0.02) compared with vehicle-treated rats (intima/media ratio, 0.92.+-.0.21) or hydralazine-treated rats with a similar blood pressure decrease (intima/media ratio, 1.03.+-.0.15). The phosphorylation of myosin phosphatase and myosin light chain was elevated in injured arteries in a Y-27632-sensitive manner, indicating the augmentation of ROCK activity in neointimal formation. The downregulation of the **cyclin-dependent kinase** inhibitor **p27**(kip1) in injured vessels was reversed by Y-27632 treatment, reflecting the antiproliferative effect of ROCK inhibition in vivo. Conclusions - We

conclude that ROCK plays a key role in the process of neointimal formation after balloon injury. Thus, the inhibition of ROCK may be a potential therapeutic strategy for treating vascular **proliferative** disorders and hypertension.

L27 ANSWER 25 OF 62 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 2000253777 MEDLINE
DOCUMENT NUMBER: 20253777 PubMed ID: 10790340
TITLE: Differential effects of the **cyclin-dependent kinase** inhibitors **p27** (Kip1), p21(Cip1), and p16(Ink4) on vascular **smooth muscle** cell **proliferation.**
AUTHOR: Tanner F C; Boehm M; Akyurek L M; San H; Yang Z Y; Tashiro J; Nabel G J; Nabel E G
CORPORATE SOURCE: Departments of Internal Medicine, University of Michigan, Ann Arbor, MI, USA.
SOURCE: CIRCULATION, (2000 May 2) 101 (17) 2022-5.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20010521
Entered Medline: 20000516

AB BACKGROUND: The cyclin-dependent kinase inhibitors (CKIs) have different patterns of expression in vascular diseases. The Kip/Cip CKIs, p27(Kip1) and p21(Cip1), are upregulated during arterial repair and negatively regulate the growth of vascular smooth muscle cells (VSMCs). In contrast, the Ink CKI, p16(Ink4), is not expressed in vascular lesions. We hypothesized that a variation in the inactivation of cdk2 and cdk4 during the G(1) phase of the cell cycle by p27(Kip1), p21(Cip1), and p16(Ink4) leads to different effects on VSMC growth in vitro and in vivo. METHODS AND RESULTS: The expression of p27(Kip1) and p21(Cip1) in serum-stimulated VSMCs inactivated cdk2 and cdk4, leading to G(1) growth arrest. p16(Ink4) inhibited cdk4, but not cdk2, kinase activity, producing partial inhibition of VSMC growth in vitro. In an in vivo model of vascular injury, overexpression of p27(Kip1) reduced intimal VSMC proliferation by 52% ($P<0.01$) and the intima/media area ratio by 51% ($P<0.005$) after vascular injury and gene transfer to pig arteries, when compared with control arteries. p16(Ink4) was a weak inhibitor of intimal VSMC proliferation in injured arteries (P=NS), and it did not significantly reduce intima/media area ratios (P=NS), which is consistent with its minor effects on VSMC growth in vitro. CONCLUSIONS: p27(Kip1) and p21(Cip1) are potent inhibitors of VSMC growth compared with p16(Ink4) because of their different molecular mechanisms of cyclin-dependent kinase inhibition in the G(1) phase of the cell cycle. These findings have important implications for our understanding of the pathophysiology of vascular proliferative diseases and for the development of molecular therapies.

L27 ANSWER 26 OF 62 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 2001030510 MEDLINE
DOCUMENT NUMBER: 20498869 PubMed ID: 11042561
TITLE: p27(Kip1) loss does not predict survival in patients with advanced gastric carcinoma.
AUTHOR: Feakins R M; Mulcahy H E; Quaglia A; Jawhari A; Zhang Z; Patchett S E
CORPORATE SOURCE: Department of Histopathology and Morbid Anatomy, Queen Mary and Westfield College, University of London, Royal London

Hospital, London, United Kingdom.. rmfeakins@mds.qmw.ac.uk
SOURCE: CANCER, (2000 Oct 15) 89 (8) 1684-91.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001120

AB BACKGROUND: **p27**(Kip1) is a **cyclin-dependent kinase** inhibitor whose loss is associated with disease progression and an unfavorable outcome in several malignancies. The authors studied its expression in a consecutive series of resected gastric carcinomas. METHODS: Expression of p27(Kip1) in 71 advanced gastric **carcinomas** and 10 lymph nodes containing **metastases** was determined using an avidin-biotin-peroxidase immunohistochemical method. The relations between p27(Kip1) expression and pathologic features, patient characteristics, and survival were analyzed. RESULTS: p27(Kip1) levels in gastric carcinomas ranged from 0.63-82.97% (median, 23. 10%; mean, 27.99%). There was no association found between p27(Kip1) expression and patient gender ($P = 0.21$), patient age ($P = 0.13$), tumor stage ($P = 0.17$), tumor grade ($P = 0.22$), or histologic type ($P = 0.72$). Univariate analysis showed that long term survival was related to stage ($P < 0.0001$) and grade ($P = 0.03$). However, tumors with p27(Kip1) levels above and below the median value were associated with a similar outcome, regardless of whether all cases ($P = 0.19$) or those without metastatic disease ($P = 0.50$) or those with residual or metastatic disease ($P = 0.92$) were included. When entered into a multivariate analysis, stage ($P < 0.0001$) and grade ($P = 0.05$), but not p27(Kip1) levels ($P = 0.16$), were found to be related to patient outcome. In lymph node metastases, p27(Kip1) expression (median, 16.5%) was similar to that found in the corresponding primary lesion (median, 30.9%). CONCLUSIONS: p27(Kip1) may play a role in the pathogenesis and progression of gastric carcinoma, but its expression is unlikely to be useful as a prognostic indicator, at least in European patients with advanced disease.

L27 ANSWER 27 OF 62 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 2000270440 MEDLINE
DOCUMENT NUMBER: 20270440 PubMed ID: 10807736
TITLE: Doxazosin inhibits retinoblastoma protein phosphorylation and G(1)-->S transition in human coronary smooth muscle cells.
AUTHOR: Kintscher U; Wakino S; Kim S; Jackson S M; Fleck E; Hsueh W A; Law R E
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Diabetes and Hypertension, School of Medicine, University of California, Los Angeles, USA.
CONTRACT NUMBER: HL-58328 (NHLBI)
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (2000 May) 20 (5) 1216-24.
Journal code: B89; 9505803. ISSN: 1079-5642.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629

Entered Medline: 20000620

AB Previous studies have demonstrated that the alpha(1)-adrenergic receptor antagonist doxazosin (Dox) inhibits multiple mitogenic signaling pathways in human vascular **smooth muscle** cells. This broad antiproliferative activity of Dox occurs through a novel mechanism unrelated to its blocking the alpha(1)-adrenergic receptor. Flow cytometry demonstrated that Dox prevents mitogen-induced G(1)-->S progression of human coronary artery **smooth muscle** cells (CASMCs) in a dose-dependent manner, with a maximal reduction of S-phase transition by 88+/-10.5% in 20 ng/mL platelet-derived growth factor and 1 micromol/L insulin (P+I)-stimulated cells (P<0.01 for 10 micromol/L Dox versus P+I alone) and 52+/-18.7% for 10% FBS-induced mitogenesis (P<0.05 for 10 micromol/L Dox versus 10% FBS alone). Inhibition of G(1) exit by Dox was accompanied by a significant blockade of retinoblastoma protein (Rb) phosphorylation. Hypophosphorylated Rb sequesters the E2F transcription factor, leading to G(1) arrest. Adenoviral overexpression of E2F-1 stimulated quiescent CASMCs to progress through G(1) and enter the S phase. E2F-mediated G(1) exit was not affected by Dox, suggesting that it targets events upstream from Rb hyperphosphorylation. Downregulation of the **cyclin-dependent kinase** inhibitory protein **p27** is important for maximal activation of G(1) cyclin/cyclin-dependent kinase holoenzymes to overcome the cell cycle inhibitory activity of Rb. In Western blot analysis, p27 levels decreased after mitogenic stimulation (after P+I, 43+/-1.8% of quiescent cells [P<0.01 versus quiescent cells]; after 10% FBS, 55+/-7.7% of quiescent cells [P<0. 05 versus quiescent cells]), whereas the addition of Dox (10 micromol/L) markedly attenuated its downregulation (after P+I, 90+/-8.3% of quiescent cells [P<0.05 versus P+I alone]; after 10% FBS, 78+/-8.3% of quiescent cells [P<0.05 versus 10% FBS alone]). Furthermore, Dox inhibited cyclin A expression, an E2F regulated gene that is essential for cell cycle progression into the S phase. The present study demonstrates that Dox inhibits CASMC **proliferation** by blocking cell cycle progression from the G(0)/G(1) phase to the S phase. This G(1)-->S blockade likely results from an inhibition of mitogen-induced Rb hyperphosphorylation through prevention of p27 downregulation.

L27 ANSWER 28 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000315630 EMBASE

TITLE: Overexpression of .alpha.1.beta.1 integrin directly affects rat mesangial cell behavior.

AUTHOR: Kagami S.; Kondo S.; Urushihara M.; Loster K.; Reutter W.; Saijo T.; Kitamura A.; Kobayashi S.; Kuroda Y.

CORPORATE SOURCE: Dr. S. Kagami, Department of Pediatrics, School of Medicine, University of Tokushima, Kuramoto-cho-3-chome, Tokushima 770-8503, Japan. kagami@medclin.clin.med.tokushima-u.ac.jp

SOURCE: Kidney International, (2000) 58/3 (1088-1097).
Refs: 48
ISSN: 0085-2538 CODEN: KDYIA5

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background. Glomerular mesangial cell (MC) **proliferation**, hypertrophy, and abnormal matrix remodeling characterized by increased expression of fibronectin, laminin and collagen type IV, and neoexpression of collagen I and III are the main biological features of progressive glomerulonephritis (GN). Especially, persistent pathological matrix

remodeling may lead to glomerular scar formation (glomerular scarring). We reported recently that .alpha.1.beta.1 integrin, a major collagen receptor for MCs, may be a potential adhesion molecule for MC-mediated pathological collagen matrix remodeling in GN. Methods. To address further the direct role of .alpha.1.beta.1 integrin in MC behavior, such as cell growth and matrix remodeling, .alpha.1.beta.1 integrin was overexpressed in MCs by transfecting an expression vector containing a full-length rat .alpha.1 integrin cDNA. Flow cytometry and immunoprecipitation analysis were applied for selection of transfectants with a stable expression of the .alpha.1 integrin subunit. The effect of .alpha.1.beta.1 integrin overexpression on MC biology was examined with a 3H-thymidine incorporation assay, flow cytometric analysis of cell size and DNA content, Western blot analysis of a **cyclin-dependent-kinase** inhibitor, **p27**(Kip1) .alpha.-**smooth muscle** actin expression, and a collagen gel contraction assay. Results. The .alpha.1 transfectants displayed a dramatic inhibition of 3H-thymidine incorporation as compared with the mock transfectants. Increased expression of the .alpha.1 subunit inversely correlated with cell cycle progression and paralleled the expression of p27(Kip1) and .alpha.-**smooth muscle** actin, as well as the cell size in MCs. In addition, the .alpha.1-transfectants were able to enhance collagen matrix reorganization effectively. Conclusion. These results indicate that MC-.alpha.1.beta.1 integrin expression is a critical determinant of MC phenotypes, including cell growth, cell size, and collagen matrix remodeling ability, and thereby contributes to scar matrix remodeling (sclerosis) in GN.

L27 ANSWER 29 OF 62 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 2000257974 MEDLINE
DOCUMENT NUMBER: 20257974 PubMed ID: 10796881
TITLE: p27(Kip1) expression in normal epithelia, precancerous lesions, and carcinomas of the gallbladder: association with cancer progression and prognosis.
AUTHOR: Hui A M; Li X; Shi Y Z; Torzilli G; Takayama T; Makuuchi M
CORPORATE SOURCE: Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Japan.. amhui-tky@umin.ac.jp
SOURCE: HEPATOLOGY, (2000 May) 31 (5) 1068-72.
Journal code: GBZ; 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518

AB **p27**(Kip1) is a **cyclin-dependent kinase** inhibitor that negatively regulates cell proliferation. This study was designed to evaluate the roles of p27(Kip1) in gallbladder carcinogenesis and the prognostic value of p27(Kip1) in patients with gallbladder carcinoma. p27(Kip1) expression was examined immunohistochemically in surgically resected specimens of 8 normal epithelia, 8 adenomyomatosis lesions, 6 precancerous adenomas, and 37 carcinomas of the gallbladder. Decreased p27(Kip1) expression (<50% nuclear staining) was observed in 16 of the 37 (43%) gallbladder carcinomas, but not in any specimen of normal epithelium, adenomyomatosis, or adenoma. The fact that all of the adenomas showed normal p27(Kip1) expression suggests that decreased p27(Kip1) expression is probably not an early event in gallbladder carcinogenesis. Decreased p27(Kip1) expression

was significantly associated with less marked tumor cell differentiation (P =.017), lymphatic invasion (P =.046), lymph node metastasis (P =.007), and advanced TNM stage (stage IV vs. stage I, P =.026; stage IV vs. stage II, P =.005). This suggests that down-regulation of p27(Kip1) expression is a late event in gallbladder **carcinogenesis**, possibly promoting **tumor** progression and **metastasis**.
Kaplan-Meier curves showed that decreased p27(Kip1) expression was significantly associated with shorter overall survival (P =.001) in patients with gallbladder carcinomas who had undergone radical surgery. Cox's proportional hazards model revealed decreased p27(Kip1) expression to be an independent predictor for death (P =.034; risk ratio, 3.9; 95% confidence interval, 1.1-13.7). In conclusion, decreased p27(Kip1) expression significantly correlates with tumor progression and predicts poor prognosis in gallbladder carcinomas.

L27 ANSWER 30 OF 62 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 2000175921 MEDLINE
DOCUMENT NUMBER: 20175921 PubMed ID: 10710342
TITLE: Physiological cyclic stretch causes cell cycle arrest in cultured vascular smooth muscle cells.
AUTHOR: Chapman G B; Durante W; Hellums J D; Schafer A I
CORPORATE SOURCE: Department of Bioengineering, Rice University, Houston, TX 77005, USA.
CONTRACT NUMBER: HL-18584 (NHLBI)
HL-36045 (NHLBI)
HL-59976 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. HEART AND CIRCULATORY PHYSIOLOGY, (2000 Mar) 278 (3) H748-54.
Journal code: DKM; 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000407

AB **Smooth muscle** cells (**SMC**) are the major cellular component of the blood vessel wall and are continuously exposed to cyclic stretch due to pulsatile blood flow. This study examined the effects of a physiologically relevant level of cyclic stretch on rat aortic vascular **SMC proliferation**. Treatment of static **SMC** with serum, platelet-derived growth factor, or thrombin stimulated **SMC proliferation**, whereas exposure of **SMC** to cyclic stretch blocked the **proliferative** effect of these growth factors. The stretch-mediated inhibition in **SMC** growth was not due to cell detachment or increased cell death. Flow cytometry analysis revealed that cyclic stretch increased the fraction of **SMC** in the G(0)/G(1) phase of the cell cycle. Stretch-inhibited G(1)/S phase transition was associated with a decrease in retinoblastoma protein phosphorylation and with a selective increase in the **cyclin-dependent kinase** inhibitor p21, but not **p27**. These results demonstrate that cyclic stretch inhibits **SMC** growth by blocking cell cycle progression and suggest that physiological levels of cyclic stretch contribute to vascular homeostasis by inhibiting the **proliferative** pathway of **SMC**.

L27 ANSWER 31 OF 62 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 2001010141 MEDLINE
DOCUMENT NUMBER: 20431929 PubMed ID: 10974218

TITLE: eNOS gene transfer to vascular smooth muscle cells inhibits cell proliferation via upregulation of p27 and p21 and not apoptosis.
COMMENT: Comment in: Cardiovasc Res. 2000 Sep;47(4):640-1
AUTHOR: Sato J; Nair K; Hiddinga J; Eberhardt N L; Fitzpatrick L A; Katusic Z S; O'Brien T
CORPORATE SOURCE: Department of Endocrinology, Mayo Clinic and Foundation, Rochester, MN 55905, USA.
CONTRACT NUMBER: HL-44116 (NHLBI)
HL-53542 (NHLBI)
HL-58080 (NHLBI)
SOURCE: CARDIOVASCULAR RESEARCH, (2000 Sep) 47 (4) 697-706.
Journal code: COR. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001024

AB OBJECTIVE: **Smooth muscle** cell (**SMC**) **proliferation** is a critical component of vascular diseases such as atherosclerosis and restenosis. Nitric oxide (NO) donors and gene transfer of endothelial nitric oxide synthase (eNOS) have been shown to inhibit **SMC proliferation**. NO may cause this effect by delaying cell cycle progression and/or induction of apoptosis. The aim of the current study was to examine the mechanism of eNOS-mediated inhibition of **SMC proliferation**. In addition, the effect of eNOS expression in vascular SMCs on the expression of the **cyclin dependent kinase** inhibitors, **p27** and p21 was examined. METHODS: SMCs were transduced with an adenoviral vector encoding eNOS (AdeNOS) or beta-galactosidase (Ad beta Gal) at a multiplicity of infection of 100. Non-transduced cells served as additional controls. Transgene expression was sought by NADPH diaphorase staining, immunohistochemistry and Western Blotting. Functionality of the recombinant protein was assessed by measurement of cGMP. Cell cycle analysis was performed by flow cytometry and p27 and p21 expression were studied by western blot analysis. Apoptosis was sought by Annexin V staining and DNA laddering. RESULTS: eNOS expression was detected in transduced SMCs. cGMP levels were increased in eNOS-transduced compared to control cells. Expression of eNOS in SMCs resulted in a delay in cell cycle progression and upregulation of p27 and p21. There was no increase in apoptosis detected in eNOS transduced cells after 24 or 72 h. CONCLUSION: eNOS gene transfer to vascular SMCs inhibits cell **proliferation** via upregulation of p27 and p21 resulting in a delay in cell cycle progression.

L27 ANSWER 32 OF 62 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 2000164594 MEDLINE
DOCUMENT NUMBER: 20164594 PubMed ID: 10699950
TITLE: Apigenin inhibits endothelial-cell proliferation in G(2)/M phase whereas it stimulates smooth-muscle cells by inhibiting P21 and P27 expression.
AUTHOR: Trochon V; Blot E; Cymbalista F; Engelmann C; Tang R P; Thomaidis A; Vasse M; Soria J; Lu H; Soria C
CORPORATE SOURCE: INSERM U353, Institut d'Hematologie, Hopital Saint-Louis, Universite Paris 7, Paris, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (2000 Mar 1) 85 (5) 691-6.
Journal code: GQU; 0042124. ISSN: 0020-7136.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000322

AB Apigenin is a plant flavonoid that is thought to play a role in the prevention of carcinogenesis. However, its mechanism of action has not yet been elucidated. Because of the importance of angiogenesis in tumor growth, we investigated the effect of apigenin on endothelial and **smooth-muscle** cells in an in vitro model. Apigenin markedly inhibited the **proliferation**, and, to a lesser degree, the **migration** of endothelial cells, and capillary formation in vitro, independently of its inhibition of hyaluronidase activity. In contrast, it strongly stimulated vascular **smooth-muscle** -cell **proliferation**. The molecular mechanisms of apigenin activity were analyzed in these 2 types of cells. Our results show that apigenin inhibits endothelial-cell **proliferation** by blocking the cells in the G(2)/M phase as a result of the accumulation of the hyperphosphorylated form of the retinoblastoma protein. Apigenin stimulation of **smooth-muscle** cells was attributed to the reduced expression of 2 **cyclin-dependent kinase** inhibitors, p21 and **p27**, which negatively regulate the G(1)-phase cyclin-dependent kinase.

L27 ANSWER 33 OF 62 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 2000156450 MEDLINE
DOCUMENT NUMBER: 20156450 PubMed ID: 10692028
TITLE: Reduced expression of the cell-cycle inhibitor p27Kip1 is associated with progression and lymph node metastasis of gastric carcinoma.
AUTHOR: Kim D H; Lee H I; Nam E S; Shin H S; Sohn J H; Park C H; Yoon D S; Song S Y; Park Y E
CORPORATE SOURCE: Department of Pathology, College of Medicine, Hallym University, Seoul, Korea.. dhk@www.hallym.or.kr
SOURCE: HISTOPATHOLOGY, (2000 Mar) 36 (3) 245-51.
Journal code: GB4; 7704136. ISSN: 0309-0167.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000509

AB AIMS: p27Kip1 (**p27**), a **cyclin-dependent kinase** inhibitor, plays an important role as inhibiting the progression of the cell cycle. Decreased expression of p27 is associated with high histological grade and aggressiveness of several human tumours. We aimed to evaluate the role of p27 in the progression and **metastasis** of gastric **carcinoma**. METHODS AND RESULTS: We analysed the expression of p27 in 67 primary gastric **carcinomas** and 31 lymph node **metastases** by immunohistochemistry. Reduced expression of p27 was found more frequently in advanced gastric cancer (40.9%) than in early gastric cancer (15.6%) ($P < 0.001$). Decreased p27 expression correlated with large tumour size, high histological grade, lymphatic invasion, advanced stage, deep invasion, lymph node metastasis

and recurrence. The expression of p27 showed an inverse correlation with the Ki67 labelling index. There was a significant reduction of p27 expression in **metastatic tumour** cells in lymph nodes (mean positive cells: 3. 7%) when compared to the corresponding primary gastric carcinomas (mean positive cells: 8.1%) (P = 0.008). CONCLUSIONS: Alterations of p27 expression may play an important role in the progression and **metastasis** to lymph node of **tumour** cells in human gastric carcinoma.

L27 ANSWER 34 OF 62 CANCERLIT
ACCESSION NUMBER: 2000175921 CANCERLIT
DOCUMENT NUMBER: 20175921
TITLE: Physiological cyclic stretch causes cell cycle arrest in cultured vascular smooth muscle cells.
AUTHOR: Chapman G B; Durante W; Hellums J D; Schafer A I
CORPORATE SOURCE: Department of Bioengineering, Rice University, Houston, TX 77005, USA.
CONTRACT NUMBER: HL-59976 (NHLBI)
HL-18584 (NHLBI)
HL-36045 (NHLBI)
SOURCE: Am J Physiol Heart Circ Physiol, (2000). Vol. 278, No. 3 H748-54.
Journal code: DKM. ISSN: 0363-6135.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 20175921
ENTRY MONTH: 200005
AB **Smooth muscle** cells (**SMC**) are the major cellular component of the blood vessel wall and are continuously exposed to cyclic stretch due to pulsatile blood flow. This study examined the effects of a physiologically relevant level of cyclic stretch on rat aortic vascular **SMC proliferation**. Treatment of static **SMC** with serum, platelet-derived growth factor, or thrombin stimulated **SMC proliferation**, whereas exposure of **SMC** to cyclic stretch blocked the **proliferative** effect of these growth factors. The stretch-mediated inhibition in **SMC** growth was not due to cell detachment or increased cell death. Flow cytometry analysis revealed that cyclic stretch increased the fraction of **SMC** in the G(0)/G(1) phase of the cell cycle. Stretch-inhibited G(1)/S phase transition was associated with a decrease in retinoblastoma protein phosphorylation and with a selective increase in the **cyclin-dependent kinase** inhibitor p21, but not **p27**. These results demonstrate that cyclic stretch inhibits **SMC** growth by blocking cell cycle progression and suggest that physiological levels of cyclic stretch contribute to vascular homeostasis by inhibiting the **proliferative** pathway of **SMC**.

L27 ANSWER 35 OF 62 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 1999233996 MEDLINE
DOCUMENT NUMBER: 99233996 PubMed ID: 10217658
TITLE: Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle.
AUTHOR: Gallo R; Padurean A; Jayaraman T; Marx S; Roque M; Adelman S; Chesebro J; Fallon J; Fuster V; Marks A; Badimon J J
CORPORATE SOURCE: Cardiovascular Biology Research Laboratory, the Zena and Michael Wiener Cardiovascular Institute, Department of Pathology, Mount Sinai School of Medicine, New York, NY, USA.

CONTRACT NUMBER: HL-56180 (NHLBI)
P50-HL-54469 (NHLBI)
RO1-AI-39794 (NIAID)
SOURCE: CIRCULATION, (1999 Apr 27) 99 (16) 2164-70.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20010521
Entered Medline: 19990517

AB BACKGROUND: Although percutaneous transluminal coronary angioplasty (PTCA) is a highly effective procedure to reduce the severity of stenotic coronary atherosclerotic disease, its long-term success is significantly limited by the high rate of restenosis. Several cellular and molecular mechanisms have been implicated in the development of restenosis post-PTCA, including vascular **smooth muscle** cell (VSMC) activation, **migration**, and **proliferation**. Recently, our group demonstrated that rapamycin, an immunosuppressant agent with antiproliferative properties, inhibits both rat and human VSMC **proliferation** and **migration** in vitro. In the present study, we investigated (1) whether rapamycin administration could reduce neointimal thickening in a porcine model of restenosis post-PTCA and (2) the mechanism by which rapamycin inhibits VSMCs in vivo. METHODS AND RESULTS: PTCA was performed on a porcine model at a balloon/vessel ratio of 1.7+/-0.2. Coronary arteries were analyzed for neointimal formation 4 weeks after PTCA. Intramuscular administration of rapamycin started 3 days before PTCA at a dose of 0.5 mg/kg and continued for 14 days at a dose of 0.25 mg/kg. **Cyclin-dependent kinase** inhibitor (CDKI) **p27**(kip1) protein levels and pRb phosphorylation within the vessel wall were determined by immunoblot analysis. PTCA in the control group was associated with the development of significant luminal stenosis 4 weeks after the coronary intervention. Luminal narrowing was a consequence of significant neointimal formation in the injured areas. Rapamycin administration was associated with a significant inhibition in coronary stenosis (63+/-3.4% versus 36+/-4.5%; P<0.001), resulting in a concomitant increase in luminal area (1.74+/-0.1 mm2 versus 3. 3+/-0.4 mm2; P<0.001) after PTCA. Inhibition of **proliferation** was associated with markedly increased concentrations of the p27(kip1) levels and inhibition of pRb phosphorylation within the vessel wall. CONCLUSIONS: Rapamycin administration significantly reduced the arterial **proliferative** response after PTCA in the pig by increasing the level of the CDKI p27(kip1) and inhibition of the pRb phosphorylation within the vessel wall. Therefore, pharmacological interventions that elevate CDKI in the vessel wall and target cyclin-dependent kinase activity may have a **therapeutic** role in the **treatment** of **restenosis** after angioplasty in humans.

L27 ANSWER 36 OF 62 MEDLINE DUPLICATE 29

ACCESSION NUMBER: 1999261954 MEDLINE
DOCUMENT NUMBER: 99261954 PubMed ID: 10330227

TITLE: NOS gene transfer inhibits expression of cell cycle regulatory molecules in vascular smooth muscle cells.

AUTHOR: Sharma R V; Tan E; Fang S; Gurjar M V; Bhalla R C
CORPORATE SOURCE: Department of Anatomy and Cell Biology and The Cardiovascular Center, The University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.

CONTRACT NUMBER: HL-14388 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 May) 276 (5 Pt 2) H1450-9.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990603

AB The mechanisms of nitric oxide (NO)-mediated inhibition of vascular **smooth muscle** (VSM) cell **proliferation** are still obscure. Cyclins A and E in association with cyclin-dependent kinase 2 (cdk2) serve as positive regulators for mammalian cell cycle progression through the G1/S checkpoint of the cell cycle and subsequent cell **proliferation**. Therefore, we have tested the effect of adenovirus-mediated transfection of the endothelial nitric oxide synthase (eNOS) gene into guinea pig coronary VSM cells on platelet-derived growth factor (BB homodimer) (PDGF-BB)-stimulated cell **proliferation** and the expression of cell cycle regulatory molecules. Transfection of the eNOS gene (eNOS) into VSM cells significantly inhibited ($P < 0.05$) [3H]thymidine incorporation into the DNA in response to PDGF-BB stimulation compared with lacZ-transfected control cells. The eNOS transfer significantly inhibited ($P < 0.05$) PDGF-BB-induced **proliferating** cell nuclear antigen (PCNA) and cyclin A expression in VSM cells compared with cells transfected with the control vector. The time course of cyclin E expression in response to PDGF-BB stimulation was delayed in eNOS-transfected cells. Levels of **cyclin-dependent kinase** inhibitors p21 and **p27** were not significantly affected by eNOS transfer. eNOS transfer did not decrease PDGF-beta receptor number, affinity, and autophosphorylation measured by radioreceptor assay and Western analysis. These results suggest that inhibition of PDGF-stimulated expression of cyclin A, cyclin E, and PCNA is the target of NO action. These findings could explain, at least in part, NO-mediated inhibition of VSM cell **proliferation**.

L27 ANSWER 37 OF 62 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 1999445331 MEDLINE
DOCUMENT NUMBER: 99445331 PubMed ID: 10514396
TITLE: Loss of cell cycle regulators p27(Kip1) and cyclin E in transitional cell carcinoma of the bladder correlates with tumor grade and patient survival.
AUTHOR: Del Pizzo J J; Borkowski A; Jacobs S C; Kyprianou N
CORPORATE SOURCE: Division of Urology, Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.
CONTRACT NUMBER: DK 53525-02 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1999 Oct) 155 (4) 1129-36.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991104

AB The **cyclin-dependent kinase** inhibitor

p27(Kip1) is a powerful molecular determinant of cell cycle progression. Loss of expression of p27(Kip1) has been shown to be predictive of disease progression in several human malignancies. In this study we investigated the expression of two key cell cycle regulators, p27(Kip1) and cyclin E, in the progression of transitional cell carcinoma of the bladder. An immunohistochemical analysis was conducted in a series of 50 bladder **tumor** specimens, including 3 **metastatic** lymph nodes, and 7 normal bladder specimens, using specific antibodies against the two regulators of the cell cycle, p27(Kip1) and cyclin E. The degree of immunoreactivity was correlated with the pathological tumor grade, stage, and patient survival. A uniformly intense immunoreactivity for p27(Kip1) and cyclin E was observed in epithelial cells of normal bladder tissue. Malignant bladder tissue demonstrated a heterogeneous pattern of significantly reduced p27(Kip1) and cyclin E immunoreactivity, compared with normal urothelium ($P < 0.01$). In addition, there was progressive loss of expression of both cell cycle proteins with increasing tumor grade and pathological stage. Expression of p27(Kip1) was significantly lower in the poorly differentiated tumors (grades III) compared to well and moderately differentiated (grades I and II) tumors ($P = 0.004$). Moreover, the expression of cyclin E was lower in grade III tumors compared to grade I and II lesions, although this difference failed to reach statistical significance. Most significantly, Kaplan-Meier plots of patient survival show increased mortality risk associated with low levels of p27(Kip1) ($P = 0.001$) and cyclin E ($P = 0.002$) expression. This is the first evidence that loss of expression of p27(Kip1) and cyclin E in human bladder transitional cell carcinoma cells correlates with advancing histological aggressiveness and poor patient survival. These results have clinical importance, because they support a role for p27(Kip1) and cyclin E as novel predictive markers of the biological potential of bladder tumors that will enable identification of those tumors most likely to progress to muscle invasive disease and of patient survival.

L27 ANSWER 38 OF 62 MEDLINE DUPLICATE 31
ACCESSION NUMBER: 1999190203 MEDLINE
DOCUMENT NUMBER: 99190203 PubMed ID: 10091782
TITLE: Low p27 expression correlates with poor prognosis for patients with oral tongue squamous cell carcinoma.
AUTHOR: Mineta H; Miura K; Suzuki I; Takebayashi S; Amano H; Araki K; Harada H; Ichimura K; Wennerberg J P; Dictor M R
CORPORATE SOURCE: Department of Otolaryngology, Hamamatsu University School of Medicine, Japan.
SOURCE: CANCER, (1999 Mar 1) 85 (5) 1011-7.
Journal code: CLZ; 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990420
Last Updated on STN: 19990420
Entered Medline: 19990407

AB BACKGROUND: **p27**, a **cyclin-dependent kinase** inhibitor, regulates progression from G1 to S phase. There have been a few clinical reports of low p27 expression associated with poor survival among patients with cancer; however, there have been no reports of such an association in cases of head and neck cancer. The authors investigated whether p27 expression in patients with oral tongue squamous cell carcinoma was associated with their prognosis. METHODS: Ninety-four patients with oral tongue squamous cell carcinoma were analyzed. The authors performed p27 immunohistochemistry on all patients

and Western blot analysis on 19 available patients. Cox proportional hazards regression analysis that included gender, history of smoking and alcohol usage, presence of multiple primary cancers, stage, histologic grade, and p27 status was used to identify the multivariate predictive value of prognostic factors. RESULTS: Twenty-six patients had high p27 expression (> or =50% tumor cell nuclei positive), and 68 patients had low p27 expression (<50%) by immunohistochemistry. In those with low p27 expression, N(+) and advanced T (T3 or T4) were significantly higher than in those with high p27 expression (P = 0.02 and 0.04). The 5-year survival rate in the low p27 group was 44%, whereas that in the high p27 group was 68%, indicating a significant difference (P = 0.04). p27 expression was inferred from Western blot analysis, and an arbitrary quantity (<1, 1-5, or > or =5) from the ratio of tumor to normal tissue density was used to characterize, resulting in 8 (42%), 3 (16%), and 8 (42%) patients in the low (<1-fold), intermediate (1-5-fold), and high (> or =5-fold) groups, respectively. Results of immunohistochemical analysis for p27 were significantly correlated with those of Western blot analysis (P = 0.02). Multivariate analysis revealed that low intensity of p27 expression and advanced stage (Stage III or IV) were predictors of reduced survival (P = 0.02 and 0.001). CONCLUSIONS: Low p27 expression was associated with increasing lymph node **metastasis** and stage of **tumor** and resulted in a poor prognosis for patients with oral tongue squamous cell carcinoma. p27 is apparently a significant predictor of survival.

L27 ANSWER 39 OF 62 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 1999437442 MEDLINE
DOCUMENT NUMBER: 99437442 PubMed ID: 10509743
TITLE: Cancer chemoprevention by tea polyphenols through mitotic signal transduction blockade.
AUTHOR: Lin J K; Liang Y C; Lin-Shiau S Y
CORPORATE SOURCE: Institute of Biochemistry, College of Medicine, National Taiwan University, Taipei.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1999 Sep 15) 58 (6) 911-5. Ref: 28
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991008

AB Tea is a popular beverage. The consumption of green tea is associated with a lower risk of several types of cancer, including stomach, esophagus, and lung. The cancer chemopreventive effect of tea has been attributed to its major phytopolyphenols. The tea polyphenols comprise about one-third of the weight of the dried leaf, and they show profound biochemical and pharmacological activities including antioxidant activities, modulation of carcinogen metabolism, inhibition of cell proliferation, induction of cell apoptosis, and cell cycle arrest. They intervene in the biochemical and molecular processes of multistep carcinogenesis, comprising tumor initiation, promotion, and progression. Several studies demonstrate that most tea polyphenols exert their scavenging effects against reactive oxygen species (ROS); excessive production of ROS has been implicated for the development of **cardiovascular diseases**, neurodegenerative disorders, and cancer. Recently, we have found that the major tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) suppresses

extracellular signals and cell proliferation through epidermal growth factor receptor binding in human A431 epidermoid carcinoma cells; EGCG also blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of the transcription factor NFKB in macrophages. Furthermore, EGCG blocks the cell cycle at the G1 phase in MCF-7 cells. We have demonstrated that EGCG inhibits the activities of cyclin-dependent kinases 2 and 4; meanwhile, EGCG induces the expression of the **Cdk** inhibitors p21 and **p27**. These results suggest that tumor promotion can be enhanced by ROS and oxidative mitotic signal transduction, and this enhancement can be suppressed by EGCG or other tea polyphenols.

L27 ANSWER 40 OF 62 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 1999423695 MEDLINE
DOCUMENT NUMBER: 99423695 PubMed ID: 10491417
TITLE: A novel role for the cyclin-dependent kinase inhibitor p27(Kip1) in angiotensin II-stimulated vascular-smooth muscle cell hypertrophy.
COMMENT: Comment in: J Clin Invest. 1999 Sep;104(6):673-4
AUTHOR: Braun-Dullaeus R C; Mann M J; Ziegler A; von der Leyen H E; Dzau V J
CORPORATE SOURCE: Division of Cardiology, Giessen University, 35392 Giessen, Germany.
CONTRACT NUMBER: HL-35610 (NHLBI)
HL-58516 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1999 Sep) 104 (6) 815-23.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991013

AB Angiotensin II (Ang II) has been shown to stimulate either hypertrophy or hyperplasia. We postulated that the differential response of vascular **smooth muscle** cells (VSMCs) to Ang II is mediated by the **cyclin-dependent kinase** (**Cdk**) inhibitor **p27**(Kip1), which is abundant in quiescent cells and drops after serum stimulation. Ang II treatment (100 nM) of quiescent VSMCs led to upregulation of the cell-cycle regulatory proteins cyclin D1, Cdk2, **proliferating** cell nuclear antigen, and Cdk1. p27(Kip1) levels, however, remained high, and the activation of the G1-phase Cdk2 was inhibited as the cells underwent hypertrophy. Overexpression of p27(Kip1) cDNA inhibited serum-stimulated [(3)H]thymidine incorporation compared with control-transfected cells. This cell-cycle inhibition was associated with cellular hypertrophy, as reflected by an increase in the [(3)H]leucine/[(3)H]thymidine incorporation ratio and by an increase in forward-angle light scatter during flow cytometry at 48 hours after transfection. The role of p27(Kip1) in modulating the hypertrophic response of VSMCs to Ang II was further tested by antisense oligodeoxynucleotide (ODN) inhibition of p27(Kip1) expression. Ang II stimulated an increase in [(3)H]thymidine incorporation and the percentage of S-phase cells in antisense ODN-transfected cells but not in control ODN-transfected cells. We conclude that p27(Kip1) plays a role in mediating VSMC hypertrophy. Ang II stimulation of quiescent cells in which p27(Kip1) levels are high results in hypertrophy but promotes hyperplasia when levels of p27(Kip1) are low, as in the presence of other growth

factors.

L27 ANSWER 41 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999172891 EMBASE
TITLE: Expression of protein p27 is associated with progression and prognosis in laryngeal cancer.
AUTHOR: Fan G.-K.; Fujieda S.; Sunaga H.; Tsuzuki H.; Ito N.; Saito H.
CORPORATE SOURCE: Dr. S. Fujieda, Department of Otorhinolaryngology, Fukui Medical University, Shimoaizuki, Matsuoka 910-1193, Japan
SOURCE: Laryngoscope, (1999) 109/5 (815-820).
Refs: 21
ISSN: 0023-852X CODEN: LARYA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective: A **cyclin-dependent kinase** inhibitor, **p27**(kip1), is recognized as a negative regulator of the cell cycle. To clarify whether immunohistochemical detection of p27 might provide prognostic information, we investigated the expression of p27 in laryngeal squamous cell carcinoma (SCC). Study Design: A retrospective study of patients was performed in 109 cases of laryngeal SCC. In addition, we investigated the expression of p53 and granulocyte colony-stimulating factor receptor (GCSF-R) to examine the prognostic significance of them in the same samples. Methods: Immunohistochemical staining by specific monoclonal antibodies was performed using the avidin-biotin-peroxidase complex technique. Results: Advanced tumor size and clinical stage and the occurrence of lymph node metastasis were associated with the absence of p27 expression, but not correlated with p53 expression and GCSF-R expression. The overall 5-year survival rate in the p27-positive group was significantly higher than that in the p27-negative group. In the Cox proportional hazard model, p27 was demonstrated to be the most powerful prognostic factor among gender, **tumor** size, lymph node **metastasis**, stage of disease, and p53 and GCSF-R expression. Conclusions: We concluded that assessment of p27 expression is useful as a prognostic factor for laryngeal SCC and of value in selecting patients with laryngeal SCC for aggressive therapy.

L27 ANSWER 42 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999199624 EMBASE
TITLE: Downregulation of p27(KIP1) and Ki67/Mib1 labeling index support the classification of thyroid carcinoma into prognostically relevant categories.
AUTHOR: Tallini G.; Garcia-Rostan G.; Herrero A.; Zelterman D.; Viale G.; Bosari S.; Carcangiu M.L.
CORPORATE SOURCE: Dr. G. Tallini, Department of Pathology, Yale University School of Medicine, PO Box 208070, New Haven, CT 06520-8070, United States
SOURCE: American Journal of Surgical Pathology, (1999) 23/6 (678-685).
Refs: 48
ISSN: 0147-5185 CODEN: AJSPDX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy

016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The **cyclin-dependent kinase** inhibitor **p27**(KIP1) has been proposed as a valuable prognostic indicator for a variety of human neoplasms. Immunohistochemical reactivity for p27(KIP1) and the proliferation marker Ki67/Mib1 were investigated in 90 thyroid carcinomas of follicular cell origin. The neoplasms were divided into three prognostic groups on the basis of their morphologic features: group 1, well-differentiated papillary or follicular carcinomas with favorable pathologic features (43 papillary carcinomas and 4 minimally invasive follicular carcinomas); group 2, papillary or follicular carcinomas with unfavorable pathologic features (21 poorly differentiated carcinomas and 2 papillary carcinomas, tall cell variant); and group 3, undifferentiated, or anaplastic, carcinomas, p27(KIP1) expression (p = 0.007) and Ki67/Mib1 labeling index (p = 0.02) showed a strong correlation with the subdivision of the thyroid carcinomas in the three prognostic groups with a significant linear trend for tumors with low p27(KIP1) (p = 0.002) and high Ki67/Mib1 labeling index (p = 0.005) to segregate into the unfavorable categories (groups 2 and 3). Low p27(KIP1) expression, but not cellular proliferation, was related to adverse prognostic factors, such as large tumor size (p = 0.03) and extrathyroidal extension (p = 0.01), but the correlation was not independent of the subdivision in the three groups. Low p27(KIP1) expression (p = 0.03) and high proliferative rate (p = 0.02) were associated with poor survival, reflecting the close association between patient morbidity and mortality rates and tumor differentiation. No significant association could be seen between p27(KIP1) or cellular proliferation and clinicopathologic parameters (e.g., age, sex, tumor size, extrathyroidal extension, vascular invasion, lymph node **metastases**, distant **metastases**, **tumor** stage, and survival rate) within any of the groups, or the histologic diagnosis of papillary versus follicular carcinoma irrespective of their degree of differentiation. Modulation of p27(KIP1) and cellular proliferation patterns in thyroid carcinoma correlate with tumor differentiation and support the morphologic classification of thyroid carcinoma into prognostically relevant categories.

L27 ANSWER 43 OF 62 MEDLINE DUPLICATE 34
ACCESSION NUMBER: 1999359552 MEDLINE
DOCUMENT NUMBER: 99359552 PubMed ID: 10398122
TITLE: Expression of p27/Kip1 is down-regulated in human prostate carcinoma progression.
AUTHOR: Fernandez P L; Arce Y; Farre X; Martinez A; Nadal A; Rey M J; Peiro N; Campo E; Cardesa A
CORPORATE SOURCE: Department of Anatomical Pathology, Hospital Clinic of Barcelona and Institut d'Investigacions Biomediques 'August Pi i Sunyer' (IDIBAPS), University of Barcelona, Hospital Casa Maternitat, Barcelona, Spain..
fernandez@medicina.ub.es
SOURCE: JOURNAL OF PATHOLOGY, (1999 Apr) 187 (5) 563-6.
Journal code: JLB; 0204634. ISSN: 0022-3417.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000407
Last Updated on STN: 20000407
Entered Medline: 20000330
AB **p27**(Kip1) is a **cyclin-dependent**

kinase inhibitor whose down-regulation has been observed in several tumour models, including breast, colorectal, and gastric carcinomas. The purpose of this study was to assess p27(Kip1) protein expression in normal and benign prostatic epithelia as well as the possible existence of abnormalities in prostate carcinoma progression. p27(Kip1) expression was immunohistochemically analysed in 51 normal tissue samples, 11 nodular hyperplasias (NH), 22 high-grade prostatic intraepithelial neoplasias (PIN), 56 localized prostate adenocarcinomas, and 19 metastases. Immunoblotting was performed in ten cases. Normal prostate epithelium and NH showed diffuse and intense p27(Kip1) nuclear expression in most cases. A significant p27(Kip1) down-regulation was observed in many carcinomas when compared with benign epithelium. Forty-seven cases (84 per cent) were low p27(Kip1) expressors (<50 per cent positive cells) and nine cases (16 per cent) were high p27(Kip1) expressors. p27(Kip1) down-regulation was also consistently seen in PIN. Fourteen out of 19 metastases (74 per cent) were low p27(Kip1) expressors. Six **metastatic** samples had their corresponding primary **tumour** analysed and three cases showed decreased expression in the metastasis. It is concluded that p27(Kip1) is constitutively expressed in normal and benign prostatic tissue. This expression is clearly down-regulated in neoplastic progression from the preinvasive lesions through invasive **carcinoma** and **metastases** and this therefore occurs in early stages of neoplastic transformation.

L27 ANSWER 44 OF 62 MEDLINE DUPLICATE 35
ACCESSION NUMBER: 1999119341 MEDLINE
DOCUMENT NUMBER: 99119341 PubMed ID: 9918868
TITLE: Eicosapentaenoic acid and docosahexaenoic acid inhibit vascular smooth muscle cell proliferation by inhibiting phosphorylation of Cdk2-cyclinE complex.
AUTHOR: Terano T; Tanaka T; Tamura Y; Kitagawa M; Higashi H; Saito Y; Hirai A
CORPORATE SOURCE: Department of Internal Medicine, Chiba Municipal Hospital, 827 Inohana Chuo-Ku, Chiba, 260, Japan.. ichi-hs@city.chiba.jp
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Jan 19) 254 (2) 502-6.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990223

AB Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the form of triacylglycerol (TG) were dose dependently incorporated into phospholipid fraction of vascular **smooth muscle** cells (VSMC) and suppressed the **proliferation** of VSMC. Flow cytometric analysis demonstrated both EPA and DHA inhibited G1/S progression. EPA and DHA inhibited the phosphorylation of Cdk2 protein and Cdk2 kinase activity without altering the amount of cyclin E and **p27**(kip1) proteins and **cyclin dependent kinase** activating **kinase** activity by growth stimulation. This mechanisms remained to be clarified but this is the first report of a novel mechanisms of inhibition of DNA synthesis by EPA and DHA.

L27 ANSWER 45 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999194562 EMBASE
TITLE: Expression of p27 is associated with Bax expression and spontaneous apoptosis in oral and oropharyngeal carcinoma.
AUTHOR: Fujieda S.; Inuzuka M.; Tanaka N.; Sunaga H.; Fan G.-K.; Ito T.; Sugimoto C.; Tsuzuki H.; Saito H.
CORPORATE SOURCE: S. Fujieda, Department of Otorhinolaryngology, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Yoshida, Fukui 910-1193, Japan. sfujieda@fmsrsa.fukui-med.ac.jp
SOURCE: International Journal of Cancer, (1999) 84/3 (315-320).
Refs: 26
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **p27**(Kip1), a **cyclin-dependent kinase** inhibitor, is a negative regulator of the cell cycle, and apoptosis is a genetically encoded program of cell death. To clarify the relationship between the cell cycle and apoptosis, we investigated expression of p27, cyclin D1 and apoptosis-related proteins (p53, Bax, Bcl-2 and c-Myc) in 60 cases of oral and oropharyngeal squamous- cell carcinoma (SCC) using an immuno-histochemical approach, and evaluated spontaneous apoptosis in vivo. Our most notable finding was that spontaneous apoptosis in the p27-positive group was significantly higher than that in the p27-negative group ($p = 0.028$). In addition, the percentage of p27-positive cells was clearly correlated with that of Bax-positive cells (.gamma. = 0.288, $p = 0.028$) and with that of cyclin D1-positive cells (.gamma. = 0.416, $p = 0.002$). Expression of p27 was inversely associated with the clinical stage of total tumor progression ($p = 0.027$). However, no correlation was found between p27 expression and the following parameters: gender, **tumor** size, lymph node **metastasis**, overall survival and disease-free survival. Our results give evidence that the action of the cell-cycle regulator p27 is closely linked with apoptosis in clinical samples from patients and indicate that over- expression of p27 might induce apoptosis in cancer cells through elevation of Bax expression, thereby acting on tumor progression.

L27 ANSWER 46 OF 62 MEDLINE DUPLICATE 36
ACCESSION NUMBER: 2000099097 MEDLINE
DOCUMENT NUMBER: 20099097 PubMed ID: 10633297
TITLE: p27 cell-cycle inhibitor is inversely correlated with lymph node metastases in right-sided colon cancer.
AUTHOR: Liu D F; Ferguson K; Cooper G S; Grady W M; Willis J
CORPORATE SOURCE: Department of Pathology, University Hospitals of Cleveland, Ohio 44106, USA.
SOURCE: JOURNAL OF CLINICAL LABORATORY ANALYSIS, (1999) 13 (6) 291-5.
Journal code: JLA; 8801384. ISSN: 0887-8013.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229

Entered Medline: 20000211

AB **p27**, a **cyclin-dependent kinase** inhibitor, suppresses proliferation of normal and neoplastic cells. Expression of p27 is correlated with survival in colon cancer. To some degree, right-sided colon cancers differ biologically and clinically from left-sided colon cancers. We analyzed 41 patients with right-sided colon cancers, including 18 cases with regional lymph node metastases and 23 cases with negative lymph nodes. Immunostaining for p27 was performed on histologic sections of primary cancers and scored. Correlation of p27 protein expression with histologic parameters was performed by t-test and multivariate analysis. Decreased p27 protein expression was associated with large tumor size. As percentages of positively stained tumor cells decreased from 70 to 29%, the mean tumor size increased from 1.9 to 7.3 cm. p27 protein expression significantly decreased in primary cancers with angiolymphatic invasion or with positive lymph nodes in comparison with those without angiolymphatic invasion (26 +/- 6 vs. 44 +/- 5%, $P < 0.03$) or with negative lymph nodes (23 +/- 4 vs. 47 +/- 6%, $P < 0.003$). p27 expression was not statistically different in terms of depth of tumor invasion (T1/T2 vs. T3/T4), tumor type or tumor differentiation. Multivariate analysis revealed that low p27 expression in primary **cancers** was correlated with lymph node **metastases** ($P = 0.01$). However, it did not correlate with any other histologic parameters. In summary, decreased p27 expression was associated with an increased likelihood of lymph node **metastases** in colon **cancers**, independent of depth of tumor invasion. This implies that p27 is a potentially important predictor for **tumor metastasis** and patient's prognosis in right-sided colon cancers.

L27 ANSWER 47 OF 62 MEDLINE DUPLICATE 37
ACCESSION NUMBER: 2001453984 MEDLINE
DOCUMENT NUMBER: 21391020 PubMed ID: 11498990
TITLE: Expression of **cyclin dependent kinase** inhibitor **p27** during **proliferation** in vascular **smooth muscle** cell.
AUTHOR: Yuan Y; Xu D L; Liu Y L; Jia M Y
CORPORATE SOURCE: Department of Cardiology, Nanfang Hospital, First Military Medical University, Guangzhou 510515.
SOURCE: SHENG LI HSUEH PAO [ACTA PHYSIOLOGICA SINICA], (1999 Jun) 51 (3) 285-90.
Journal code: UPB; 20730130R. ISSN: 0371-0874.
PUB. COUNTRY: China
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010814
Last Updated on STN: 20011022
Entered Medline: 20011018

AB This study was to investigate cell cycle distribution of the vascular smooth muscle cells (VSMCs) and negative regulator of cell proliferation p27 expression caused by platelet derived growth factor BB (PDGF-BB), angiotensin II (Ang II) and arginine vasopressin (AVP). Deprived of fotal calf serum for 48 h, cultured VSMCs in quiescent condition were collected at different times after stimulation of Ang II, AVP and PDGF-BB. Cell cycle distribution and p27 expression were determined with a flow cytometer. The results showed that the protein content of VSMCs was significantly increased (43.6%) by Ang II as a result of hypertrophy, but Ang II did not lead to downregulation of p27. AVP could downregulate p27 slightly. PDGF could inhibit p27 expression significantly and cause VSMCs

hyperplasia. These results suggest that the progression of VSMCs through G1 to S phase might be brought out by the inhibition of p27 during proliferation.

L27 ANSWER 48 OF 62 MEDLINE DUPLICATE 38
ACCESSION NUMBER: 1999163752 MEDLINE
DOCUMENT NUMBER: 99163752 PubMed ID: 10065869
TITLE: Heparin inhibits proliferation of myometrial and leiomyomal smooth muscle cells through the induction of alpha-smooth muscle actin, calponin h1 and p27.
AUTHOR: Horiuchi A; Nikaido T; Ya-Li Z; Ito K; Orii A; Fujii S
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Japan.
SOURCE: MOLECULAR HUMAN REPRODUCTION, (1999 Feb) 5 (2) 139-45.
Journal code: CWO; 9513710. ISSN: 1360-9947.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990504

AB Mast cells are widely distributed in human tissues, including the human uterus. However, the function of mast cells in uterine **smooth muscle** has not been clearly established. Mast cells possess secretory granules containing such substances as heparin, serotonin, histamine and many cytokines. To help establish the role of mast cells in the human myometrium, the action of heparin was investigated using **smooth muscle** cells (**SMC**) from normal myometrium and from leiomyoma. The **proliferation** of cultured myometrial and leiomyomal **SMC** was inhibited by heparin treatment. Flow cytometric analysis showed that the population in the G1 phase of the cell cycle increased under heparin treatment. Western blotting analysis showed that markers of **SMC** differentiation such as alpha-**smooth muscle** actin (alpha-SMA), calponin h1 and **cyclin-dependent kinase** inhibitor **p27** were induced by heparin, whereas cell-cycle-related gene products from the G1 phase of the cell cycle, such as cyclin E and cdk2, were not changed. Taken together, these results indicate that heparin inhibits the **proliferation** of myometrial and leiomyomal **SMC** through the induction of alpha-SMA, calponin h1 and p27. We suggest that heparin from mast cells may induce differentiation in uterine **SMC** and may influence tissue remodelling and reconstruction during physiological and pathophysiological events.

L27 ANSWER 49 OF 62 MEDLINE DUPLICATE 39
ACCESSION NUMBER: 2000410995 MEDLINE
DOCUMENT NUMBER: 20396809 PubMed ID: 10936889
TITLE: p27 Expression, a cyclin dependent kinase inhibitor in breast carcinoma.
AUTHOR: Barbareschi M
CORPORATE SOURCE: Department of Pathology, S. Chiara Hospital, Trento, Italy.. barbareschi@tn.aziendasanitaria.trentino.it
SOURCE: ADVANCES IN CLINICAL PATHOLOGY, (1999 Oct) 3 (4) 119-27.
Ref: 56
Journal code: DD0; 9709997. ISSN: 1125-5552.
PUB. COUNTRY: Italy
Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000831

AB **p27** KIP1 is a **cyclin dependent kinase** inhibitor, which may act as a potential suppressor gene. Several lines of evidence support the hypothesis that reduced p27 KIP1 expression is related to uncontrolled cell **proliferation** and tumorigenesis. Low immunohistochemical expression of p27 KIP1 in human neoplasm seems related to tumor progression and poor prognosis. In breast cancer, low p27 is associated with high **tumour** grade and loss of oestrogen receptor, and it has been suggested that low p27 KIP1 is a powerful and independent prognostic marker of poor clinical outcome. There are however some discrepant results: a few studies, some of which conducted on large series of patients, do not support an independent role of p27 KIP1 as a prognostic marker. We are indeed faced with an intriguing hypothesis, but many more studies are needed to evaluate the real value of p27 KIP1 as a prognostic marker.

L27 ANSWER 50 OF 62 MEDLINE DUPLICATE 40
ACCESSION NUMBER: 1999359566 MEDLINE
DOCUMENT NUMBER: 99359566 PubMed ID: 10398135
TITLE: Prognostic significance of p27(Kip1) expression in colorectal cancer: a clinico-pathological characterization.
AUTHOR: Palmqvist R; Stenling R; Oberg A; Landberg G
CORPORATE SOURCE: Department of Pathology, Umea University, SE-901 87 Umea, Sweden.
SOURCE: JOURNAL OF PATHOLOGY, (1999 May) 188 (1) 18-23.
Journal code: JLB; 0204634. ISSN: 0022-3417.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000215

AB This study has evaluated the expression of the **cyclin-dependent kinase** inhibitor **p27**(Kip1) in 89 colorectal cancers (CRCs) using immunohistochemistry and has related p27 levels to clinico-pathological characteristics, **tumour cell proliferation**, and the expression of other G1-S transition regulatory proteins. Low levels of p27 were common in CRCs; 11 per cent of the tumours expressed very low levels and 44 per cent had p27 labelling indices (LIs) below 50 per cent. Except for depth of **tumour** invasion, no significant correlation was found between p27 expression and Dukes' stage, differentiation, growth pattern, **tumour** type or lymphocytic infiltration. Interestingly, tumours expressing low or very low p27 LIs were predominantly found in the right colon (p=0.026). Expression of p27 was a strong predictor of survival, both in univariate and in multivariate survival analyses; patients with tumours of p27 LI less than 50 per cent had an impaired prognosis (p=0.0069). p27 expression did not correlate with **tumour cell proliferation**, or with expression of cyclin D1 or the retinoblastoma protein (pRb). These findings support the view that p27 not merely controls cell cycle progression, but might be associated with

other mechanisms responsible for aggressive **tumour** behaviour in colorectal cancer.

L27 ANSWER 51 OF 62 MEDLINE DUPLICATE 41
ACCESSION NUMBER: 1999322452 MEDLINE
DOCUMENT NUMBER: 99322452 PubMed ID: 10393673
TITLE: Endothelin-1 potentiates human smooth muscle cell growth to PDGF: effects of ETA and ETB receptor blockade.
AUTHOR: Yang Z; Krasnici N; Luscher T F
CORPORATE SOURCE: Cardiovascular Research, Institute of Physiology, University Zurich-Irchel and Cardiology, University Hospital Zurich, Switzerland.
SOURCE: CIRCULATION, (1999 Jul 6) 100 (1) 5-8.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990730
Last Updated on STN: 20010521
Entered Medline: 19990716

AB BACKGROUND: Endothelin-1 (ET-1) is a potent vasoconstrictor. However, its mitogenic effects on vascular **smooth muscle** cells (SMCs) remain controversial. We investigated the role of ET-1 in human **SMC** growth and its synergistic effect with platelet-derived growth factor (PDGF). METHODS AND RESULTS: Human aortic SMCs were cultured and cell **proliferation** was assayed by [3H]thymidine incorporation. PDGF receptor expression, activation of mitogen-activated protein kinase (MAPK), cell cycle regulators such as **cyclin-dependent kinase** 2 (Cdk2), **Cdk** inhibitor (**p27**(Kip1)), and retinoblastoma protein (pRb) were analyzed by immunoblotting. ET-1 on its own was unable to stimulate [3H]thymidine incorporation but dramatically potentiated the effect of PDGF-BB up to 6-fold ($P<0.001$). Most of the potentiating effects (88%) were blocked by the ETA receptor antagonist LU135252 and slightly further blocked by the ETA/B receptor antagonist bosentan ($P<0.05$). ET-1 stimulated MAPK, but it neither potentiated PDGF-induced MAPK activation nor overexpressed PDGF receptors. In contrast to PDGF-BB, ET-1 had no regulatory effects on Cdk2, p27(Kip1), and pRb. CONCLUSIONS: In human SMCs, ET-1 activates MAPK but has no mitogenic effects on its own. However, ET-1 markedly potentiates **proliferation** to PDGF, mainly via ETA receptors. This may represent an important function of ET-1 for vascular structural changes in patients and provide new therapeutic opportunities for ET-1 receptor antagonists.

L27 ANSWER 52 OF 62 CANCERLIT
ACCESSION NUMBER: 1999261954 CANCERLIT
DOCUMENT NUMBER: 99261954
TITLE: NOS gene transfer inhibits expression of cell cycle regulatory molecules in vascular smooth muscle cells.
AUTHOR: Sharma R V; Tan E; Fang S; Gurjar M V; Bhalla R C
CORPORATE SOURCE: Department of Anatomy and Cell Biology and The Cardiovascular Center, The University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.
CONTRACT NUMBER: HL-14388 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999). 276 (5 Pt. 2):H1450-9.
Journal code: 3U8. ISSN: 0002-9513.

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 99261954
ENTRY MONTH: 199907

AB The mechanisms of nitric oxide (NO)-mediated inhibition of vascular **smooth muscle** (VSM) cell **proliferation** are still obscure. Cyclins A and E in association with cyclin-dependent kinase 2 (cdk2) serve as positive regulators for mammalian cell cycle progression through the G1/S checkpoint of the cell cycle and subsequent cell **proliferation**. Therefore, we have tested the effect of adenovirus-mediated transfection of the endothelial nitric oxide synthase (eNOS) gene into guinea pig coronary VSM cells on platelet-derived growth factor (BB homodimer) (PDGF-BB)-stimulated cell **proliferation** and the expression of cell cycle regulatory molecules. Transfection of the eNOS gene (eNOS) into VSM cells significantly inhibited ($P < 0.05$) [3H]thymidine incorporation into the DNA in response to PDGF-BB stimulation compared with lacZ-transfected control cells. The eNOS transfer significantly inhibited ($P < 0.05$) PDGF-BB-induced **proliferating** cell nuclear antigen (PCNA) and cyclin A expression in VSM cells compared with cells transfected with the control vector. The time course of cyclin E expression in response to PDGF-BB stimulation was delayed in eNOS-transfected cells. Levels of **cyclin-dependent kinase** inhibitors p21 and **p27** were not significantly affected by eNOS transfer. eNOS transfer did not decrease PDGF-beta receptor number, affinity, and autophosphorylation measured by radioreceptor assay and Western analysis. These results suggest that inhibition of PDGF-stimulated expression of cyclin A, cyclin E, and PCNA is the target of NO action. These findings could explain, at least in part, NO-mediated inhibition of VSM cell **proliferation**.

L27 ANSWER 53 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999015595 EMBASE
TITLE: Reduced expression of cyclin-dependent kinase inhibitor p27(Kip1) is an indicator of malignant behavior in oral squamous cell carcinoma.
AUTHOR: Kudo Y.; Takata T.; Yasui W.; Ogawa I.; Miyauchi M.; Takekoshi T.; Tahara E.; Nikai H.
CORPORATE SOURCE: Y. Kudo, Department of Oral Pathology, Hiroshima Univ. School of Dentistry, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan
SOURCE: Cancer, (15 Dec 1998) 83/12 (2447-2455).
Refs: 30
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB BACKGROUND. Reduced expression of the **cyclin-dependent kinase** inhibitor **p27**(Kip1) has been reported to correlate with poor survival in cohorts of breast and colorectal carcinoma patients. Posttranslational ubiquitin- mediated proteasomal proteolysis is related to p27(Kip1) protein levels. However, to the authors' knowledge, no previous study has examined the expression of p27(Kip1) in oral squamous cell carcinoma (OSCC). METHODS. To examine the expression of p27(Kip1) and its clinicopathologic roles in OSCC, the authors studied the expression of p27(Kip1) protein by immunohistochemistry in deparaffinized

tissue sections of 20 normal oral mucosa specimens, 22 epithelial dysplasia specimens, and 70 OSCCs, and analyzed its correlation with clinicopathologic parameters. They also studied the expression of p27(Kip1) mRNA and protein in six OSCC cell lines by Northern blot and Western blot analysis. To examine the mechanism of reduced expression of p27(Kip1), OSCC cell lines were treated with the proteasome inhibitor LLnV. RESULTS. All the normal oral mucosa specimens and 73% (16 of 22) of the oral epithelial dysplasia specimens expressed p27(Kip1) at high levels, whereas 87% of the OSCCs (61 of 70) showed reduced expression of p27(Kip1). Furthermore, the levels of expression of this protein were significantly lower in **carcinomas** with **metastasis** than those without **metastasis**. Although OSCC cell lines expressed p27(Kip1) mRNA at various levels, most of them expressed p27(Kip1) protein at lower or undetectable levels. LLnV induced the expression of p27(Kip1) protein in HSC2 cells, in which p27(Kip1) protein was originally undetectable. CONCLUSIONS. These findings suggest that 1) reduced expression of p27(Kip1) may correlate with the development and progression of OSCC and can be an indicator of malignant behavior of this neoplasm, and 2) increased proteasome-mediated degradation may play an important role in the reduction of p27(Kip1) protein expression.

L27 ANSWER 54 OF 62 MEDLINE
ACCESSION NUMBER: 1999023818 MEDLINE
DOCUMENT NUMBER: 99023818 PubMed ID: 9806742
TITLE: Accumulation of p21(Cip1/WAF1) during hyperoxic lung injury in mice.
AUTHOR: O'Reilly M A; Staversky R J; Watkins R H; Maniscalco W M
CORPORATE SOURCE: Department of Pediatrics (Neonatology), School of Medicine and Dentistry, University of Rochester, Rochester, New York.. oreillym@envmed.rochester.edu
CONTRACT NUMBER: HL 36543 (NHLBI)
SOURCE: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (1998 Nov) 19 (5) 777-85.
Journal code: AOB; 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981223

AB Hyperoxic lung injury results in decreased cell **proliferation**, DNA damage, and cell death. Because the cyclin-dependent kinase inhibitor p21(Cip1/WAF1) (p21) inhibits cell **proliferation** in G1/S, enhances DNA repair, and regulates apoptosis in some cells, we hypothesized that the expression of p21 would increase in lungs of C57Bl/6J male mice exposed to and recovered from > 95% oxygen. A low level of p21 messenger RNA (mRNA) expression was detected by Northern blot analysis of room air-exposed lungs. Exposure to hyperoxia resulted in a modest increase in p21 mRNA expression by 24 h, followed by a marked induction by 48 to 72 h. In situ hybridization revealed that p21 mRNA abundance increased in bronchiolar epithelium and in resident alveolar cells, but not in **smooth-muscle** cells or large airway epithelium. Hyperoxia increased the expression of p21 protein by 24 h and continued to increase at 48 and 72 h. Immunohistochemical staining showed that p21 protein accumulated in the bronchiolar epithelium and in alveolar regions that had increased p21 mRNA expression. In contrast, the expression of the **cyclin-dependent kinase** inhibitor **p27**(Kip1) was not altered by hyperoxia. To determine

whether p21 expression was altered during the repair process, mice were exposed to hyperoxia for 64 h and allowed to recover for up to 4 d in room air. The abundance of p21 mRNA and protein decreased by 1 to 2 d of recovery and returned to room air-exposed levels by 3 to 4 d of recovery. These findings support the concept that bronchiolar epithelial and alveolar cells damaged by hyperoxia express molecules such as p21, which may participate in regulating cell **proliferation**, DNA repair, and cell death.

L27 ANSWER 55 OF 62 MEDLINE DUPLICATE 42
ACCESSION NUMBER: 1998405424 MEDLINE
DOCUMENT NUMBER: 98405424 PubMed ID: 9736017
TITLE: Down-regulation of p27 is associated with development of colorectal adenocarcinoma metastases.
AUTHOR: Thomas G V; Szigeti K; Murphy M; Draetta G; Pagano M; Loda M
CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: CA 76584-01A1 (NCI)
CA44704-09 (NCI)
GM/CA 57587-01 (NIGMS)
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1998 Sep) 153 (3) 681-7.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 20000303
Entered Medline: 19980924

AB The **cyclin-dependent kinase** inhibitor **p27** is a negative regulator of the cell cycle and a potential tumor suppressor gene. Because we had previously demonstrated that loss of p27 protein is associated with aggressive behavior in colorectal adenocarcinomas, we used immunohistochemistry and in situ hybridization to evaluate the potential role of alterations in p27 expression in primary and metastatic colorectal adenocarcinomas. Parallel immunostaining was performed for Ki-67 and p53. We evaluated 13 cases of metachronous and 23 cases of synchronous primary and **metastatic** colorectal **tumor** pairs. In the synchronous subgroup (Stage IV tumors), 57% of the primary **tumor** and **metastases** pairs did not express p27 protein and the remainder were low expressors. In the metachronous subgroup, 54% of the primary tumors were low expressors and the remainder high expressors of p27 protein. There was a significant reduction in the expression of p27 in the metachronous metastases (mean positive cells: 14.5%) when compared to the corresponding primary tumors (mean positive cells: 41.8%), P = 0.0023. All the primary and metastatic tumors in the metachronous subgroup showed high levels of p27 mRNA expression. There was no association between loss of p27 and either Ki-67 count or p53 expression. Because p27 is known to be up-regulated when epithelial cells are grown in suspension, the down-regulation of p27 in circulating tumor cells may confer the ability to grow in an environment of altered extracellular matrix or intercellular adhesion properties, two situations which may facilitate metastases.

L27 ANSWER 56 OF 62 EMBASE
ACCESSION NUMBER: 1998307316 EMBASE
TITLE: Phosphatidylinositol 3-Kinase inhibitors block aortic

smooth muscle cell **proliferation** in mid-late G1 phase: Effect on **cyclin-dependent Kinase** 2 and the inhibitory protein **p27**(KIP1).
AUTHOR: Bacqueville D.; Casagrande F.; Perret B.; Chap H.; Darbon J.-M.; Breton-Douillon M.
CORPORATE SOURCE: M. Breton-Douillon, INSERM U 326, Institut Federatif de Recherche 30, CHU Purpan, 31059 Toulouse, France. Monique.Breton@purpan.inserm.fr
SOURCE: Biochemical and Biophysical Research Communications, (27 Mar 1998) 244/3 (630-636).
Refs: 32
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry.
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In the present study, we investigated the involvement of phosphatidylinositol 3-kinase (PI 3-kinase) activity in the progression of vascular smooth muscle cells (VSMCs) throughout the G1 phase of cell cycle. Addition of two selective inhibitors of PI 3-kinase, LY 294002 or wortmannin, to quiescent VSMCs prevented serum-induced DNA synthesis in a dose-dependent manner with IC50 of 8.7 .+-. 2.0 .mu.M and 53.9 .+-. 8.5nM, respectively. Time course studies revealed that the two PI 3-kinase inhibitors blocked VSMC proliferation in mid-late G1 phase, about 6 h before the G1/S transition. This G1 growth arrest was due, at least in part, to the reduction of the CDK2 associated kinase activity resulting mainly from the upregulation of the inhibitory protein p27(KIP1).

L27 ANSWER 57 OF 62 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:524383 BIOSIS
DOCUMENT NUMBER: PREV199900524383
TITLE: Upregulation of **cyclin-dependent kinase** inhibitor **p27** by salicylates inhibits vascular **smooth muscle proliferation.**
AUTHOR(S): Marra, Diego E.; Liao, James K.
CORPORATE SOURCE: Brigham Women's Hosp., Boston, MA USA
SOURCE: Circulation, (Oct. 27, 1998) Vol. 98, No. 17 SUPPL., pp. I599-I600.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L27 ANSWER 58 OF 62 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998090158 EMBASE
TITLE: Different proliferative properties of smooth muscle cells of human arterial and venous bypass vessels: Role of PDGF receptors, mitogen-activated protein kinase, and cyclin-dependent kinase inhibitors.
AUTHOR: Yang Z.; Oemar B.S.; Carrel T.; Kipfer B.; Julmy F.; Luscher T.F.
CORPORATE SOURCE: Dr. T.F. Luscher, University Hospital, CH-8091 Zurich, Switzerland
SOURCE: Circulation, (1998) 97/2 (181-187).

Refs: 59
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background - Internal mammary artery (IMA) bypass grafts have a higher patency than saphenous vein (SV) grafts. Intimal hyperplasia of SV grafts is due to **smooth muscle** cell (**SMC**) **proliferation** and **migration**. We hypothesized that different **SMC** growth activity exists in IMA and SV, which may explain the different patencies of arterial and venous grafts. Methods and Results - SMCs were isolated from IMA and SV by explant culture and stimulated with serum or platelet-derived growth factor-BB (PDGF-BB). Cell growth was analyzed by explant outgrowth rate, 3H-thymidine incorporation, or cell counting. PDGF receptor expression and autophosphorylation, regulation of mitogen-activated protein kinases (MAPKs), and **cyclin-dependent kinase** inhibitors (**p27**(Kip1) and p21(Cip1)) were analyzed by molecular techniques. **SMC** outgrowth from explants by serum (20%) over a 20-day period was more pronounced in SV (37 .+-. 5%) than in IMA (4 .+-. 3%; P<.001) of the same patients. Serum (10%) increased cell number more rapidly in SV (2 x 104/well to 18 .+-. 4 x 104/well; P<.05) than in IMA (2 x 104/well to 9 .+-. 4 x 104/well; P<.05) over an 8-day period. PDGF-BB (0.01 to 10 ng/mL) stimulated 3H-thymidine incorporation (1347 .+-. 470% above control levels) and increased cell number in SV (2 x 104/well to 5 .+-. 1 x 104/well; P<.05) but not in IMA. PDGF .alpha.- and .beta.-receptors were similarly expressed and were activated in both SV and IMA. PDGF-BB induced a similar MAPK activation (kinetics and maximal activity) in both SV and IMA cells but increased MAPK protein level only in SV. Furthermore, PDGF-BB markedly downregulated the cell cycle inhibitor p27(Kip1) in SV, but this was much less pronounced in IMA. Conclusions - SMCs from SVs exhibit enhanced **proliferation** compared with IMA in spite of functional growth factor receptor expression and MAPK activation. However, PDGF increased MAPK protein level only in SV and downregulated cell cycle inhibitor (p27(Kip1)) more potently in SV than in IMA. This may explain the resistance to growth stimuli of IMA SMCs and may contribute to the longer patency of arterial versus venous grafts.

L27 ANSWER 59 OF 62 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 43

ACCESSION NUMBER: 1997:489339 BIOSIS
DOCUMENT NUMBER: PREV199799788542
TITLE: Reduced expression of cyclin-dependent kinase inhibitor p27-Kip1 is associated with advanced stage and invasiveness of gastric carcinomas.
AUTHOR(S): Yasui, Wataru; Kudo, Yasusei; Semba, Shuho; Yokozaki, Hiroshi; Tahara, Eiichi (1)
CORPORATE SOURCE: (1) First Dep. Pathol., Hiroshima Univ. Sch. Med., 1-2-3 Kasumi, Minami-ku, Hiroshima 734 Japan
SOURCE: Japanese Journal of Cancer Research, (1997) Vol. 88, No. 7, pp. 625-629.
ISSN: 0910-5050.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Reduced expression of a **cyclin-dependent kinase** inhibitor **p27**-Kip1 has recently been shown to predict poor survival of patients with breast and colorectal cancers. We

studied the expression of p27-Kip1 in gastric carcinomas by northern blotting, western blotting and immunohistochemistry to determine whether lack of p27 has implications for aggressiveness of gastric cancer. Reduced expression of p27 was detected in 40% of the gastric carcinomas at the mRNA level, while it was detected in 57% at the protein level. No gross alterations of the p27 gene were observed in any of the cases examined by Southern blot analysis. Immunohistochemical studies revealed that the expression of p27 was well preserved in most of the gastric adenomas, whereas it was so in only 26% of the gastric carcinomas. Fifty-six percent of the carcinomas showed almost no p27-positive cells. Decrease of p27-positive cells significantly correlated with advanced stage, depth of **tumor** invasion and lymph node **metastasis**. The expression of p27 showed an inverse correlation with the expression of cyclin E. These findings suggest that reduction of p27-Kip1 protein may reflect the progression of gastric carcinomas and may be an indicator of high-grade malignancy.

L27 ANSWER 60 OF 62 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:241383 BIOSIS
DOCUMENT NUMBER: PREV199799540586
TITLE: Regulation of vascular **smooth muscle** cell **proliferation** by the **cyclin**-**dependent kinase** inhibitor **P27** -KIP1.
AUTHOR(S): Braun-Dullaeus, R. C.; Mann, M. J.; Von Der Leyen, H. E.; Zhang, L.; Dzau, V. J.
CORPORATE SOURCE: Brigham and Women's Hosp., Dep. Med., Harvard Med. Sch., Boston, MA USA
SOURCE: Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 224A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research: Biomedicine '97 Medical Research from Bench to Bedside Washington, D.C., USA April 25-27, 1997
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L27 ANSWER 61 OF 62 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:184581 BIOSIS
DOCUMENT NUMBER: PREV199799483784
TITLE: Loss of p27-Kip1 and induction of Cdk1 in the rat carotid artery following balloon catheter injury. In vivo and in vitro influence of rapamycin.
AUTHOR(S): Braun-Dullaeus, R. C. (1); Von Der Leyen, H. E.; Mann, M. J. (1); Zhang, L. (1); Morris, R. E.; Dzau, V. J. (1)
CORPORATE SOURCE: (1) Dep. Med., Brigham and Women's Hosp., Boston, MA USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 3, pp. A153.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 97 New Orleans, Louisiana, USA April 6-9, 1997
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L27 ANSWER 62 OF 62 CANCERLIT
ACCESSION NUMBER: 97604861 CANCERLIT
DOCUMENT NUMBER: 97604861
TITLE: Blockade of epidermal growth factor receptor (EGFR) by

anti-EGFR monoclonal antibody (mAb225) induces GI arrest in prostatic cancer cell line DU145 (Meeting abstract).
AUTHOR: Peng D; Fan Z; Lu Y; DeBlasio T; Scher H; Mendelsohn J
CORPORATE SOURCE: Lab. Receptor Biology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1996). Vol. 37, pp. A1664.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199703

AB Autocrine production of epidermal growth factor (EGF) and overexpression of its receptor (EGFR) have been implicated in contributing to hormone-refractory prostatic cancer growth and successful proliferation of prostate **cancers** at **metastatic** sites. Previously, we showed that mAb225, a blocking monoclonal antibody against human EGFR, inhibited the growth of cultured DU145 human prostate cancer cells. It also inhibited DU145 xenografts growth in nude mice. Here we explored the hypothesis that mAb225 may act by interfering cell cycle traversal in the DU145 cells. Addition of mAb225 to DU145 cells induced arrest in G1 phase. This G1 arrest was found to be correlated with a sustained increase in **cyclin dependent kinase** (**Cdk**) inhibitor **p27**-kip1, at both messenger RNA and protein levels. The increase in p27 protein did not change the amount of Cdk4-bound p27, whereas Cdk2-associated p27 was increased. Cdk2-associated histone H1 kinase activity was decreased. In addition, cyclin A- and E-associated H1 kinase activities were also decreased. These studies demonstrated that the anti-proliferative effect of mAb225 on DU145 cells is at least partially a result of G1 arrest. Furthermore, this study documented that the regulation of p27 can be at both the RNA and protein levels. We are currently investigating if p27 is necessary and sufficient for the G1 arrest induced by mAb225 blockade of EGFR.

FILE 'MEDLINE' ENTERED AT 13:16:03 ON 24 MAY 2002
L28 3744 SEA (CYCLIN DEPENDENT KINASES)/CT
L29 147138 SEA (CELL MIGRATION OR ARTERIOSCLEROSIS OR CARDIOVASCULAR DISEASE OR NEOPLASM METASTASIS)/CT
L30 42 SEA L28 AND L29
L31 0 SEA L30 AND PROTEINS/CT
L32 0 SEA L30 AND ADMINISTRATION & DOSAGE/CT

FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 13:43:39 ON 24 MAY 2002
L33 227 S ("MARKS ANDREW"/AU OR "MARKS ANDREW R"/AU)
L34 64 S "MARX STEVEN O"/AU
L35 64 S L33 AND L34
L36 0 S L35 AND (L10 OR L27)
L37 227 S L33 OR L34
L38 1 S L37 AND (L10 OR L27)
L39 1460 S MARKS A?/AU
L40 1343 S MARX S?/AU
L41 105 S L39 AND L40
L42 7 S L41 AND L4
L43 3 S L42 NOT (L10 OR L27)
L44 2 DUP REMOVE L43 (1 DUPLICATE REMOVED)

=> d l44 ibib abs 1-2

L44 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
ACCESSION NUMBER: 1997:15651 BIOSIS
DOCUMENT NUMBER: PREV199799314854
TITLE: Rapamycin resistance tied to defective regulation of p27-Kip1.
AUTHOR(S): Luo, Yan; **Marx, Steven O.**; Kiyokawa, Hiroaki; Koff, Andrew; Massague, Joan; **Marks, Andrew R. (1)**
CORPORATE SOURCE: (1) Box 1269, Mount Sinai Sch. Med., One Gustave L. Levy Place, New York, NY 10029 USA
SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 12, pp. 6744-6751.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The potent antiproliferative activity of the macrolide antibiotic rapamycin is known to involve binding of the drug to its cytosolic receptor, FKBP12, and subsequent interaction with targets or rapamycin, resulting in inhibition of p70 S6 kinase (p70-S6K). However, the downstream events that lead to inhibition of cell cycle progression remain to be elucidated. The antiproliferative effects of rapamycin are associated with prevention of mitogen-induced downregulation of the **cyclin-dependent kinase** inhibitor **p27** -Kip1, suggesting that the latter may play an important role in the growth pathway targeted by rapamycin. Murine BC3H1 cells, selected for resistance to growth inhibition by rapamycin, exhibited an intact p70-S6K pathway but had abnormally low p27 levels that were no longer responsive to mitogens or rapamycin. Fibroblasts and T lymphocytes from mice with a targeted disruption of the p27-Kip1 gene had impaired growth-inhibitory responses to rapamycin. These results suggest that the ability to regulate p27-Kip1 levels is important for rapamycin to exert its antiproliferative effects.

L44 ANSWER 2 OF 2 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-255941 [30] WPIDS
DOC. NO. CPI: C2002-076291
TITLE: New isolated and/or recombinant ubiquitin ligase such as SIP (SKP Interacting Protein) ligase, for treating diseases associated with aberrant protein degradation, cell proliferation, differentiation, and cell survival.
DERWENT CLASS: B04 D16
INVENTOR(S): CALIGIURI, M; ROLFE, M
PATENT ASSIGNEE(S): (CALI-I) CALIGIURI M; (ROLF-I) ROLFE M
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002025569	A1	20020228	(200230)*		44

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002025569	A1	US 1997-915048	19970820

PRIORITY APPLN. INFO: US 1997-915048 19970820
AN 2002-255941 [30] WPIDS
AB US2002025569 A UPAB: 20020513
NOVELTY - An isolated and/or recombinant ubiquitin ligase (I), such as SIP

(SKP Interacting Protein) ligase, for example isolated and/or recombinant cdc4 polypeptide comprising a sequence identical or homologous to a sequence (S1) comprising 1121 or 162 amino acids, given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) comprising a sequence encoding a cdc4 polypeptide or its portion, or a complement or (II);

(2) an isolated nucleic acid (III) comprising a sequence encoding a vertebrate SIP polypeptide;

(3) an expression vector (IV) capable of replicating in a prokaryotic or eukaryotic cell comprising (IV);

(4) a host cell (V) transfected with (IV) and expressing (I);

(5) production of (I);

(6) a transgenic animal (VI) having cells which harbor a transgene comprising (II) or (III), or in which a gene comprising (II) or (III) is disrupted;

(7) an isolated nucleic acid (VII) which selectively hybridizes under high stringency conditions to at least 10 nucleotides of a sequence (S2) comprising 3363 or 484 base pairs, given in the specification, or its complement, where (VII) can specifically detect or amplify a sequence of a vertebrate cdc4 gene;

(8) a reconstituted protein mixture (VIII) comprising an SIP polypeptide and a cell-cycle regulatory protein;

(9) an isolated SIP polypeptide (IX) having a ubiquitin group attached to cysteine;

(10) an assay (M1) for identifying an inhibitor of an SIP-mediated ubiquitination;

(11) an assay (M2) for identifying an inhibitor of an interaction between a substrate polypeptide and a SIP protein;

(12) diagnosing (M3) a hyperproliferative disorder in a patient where the disorder is associated with the destabilization of a CKI protein in cells of the patient, by ascertaining the level of expression of a SIP ligase in a sample of cells from the patient, and diagnosing the presence or absence of hyperproliferative disorder utilizing, at least in part, the ascertained level expression or activity of the ligase, where an increase level of a SIP protein or SIP ligase activity in the sample, relative to a normal control sample of cells, correlates with the presence of a hyperproliferative disorder; and

(13) a prognostic method (M4) for evaluating the aggressiveness and/or rate of recurrence of a disorder marked by aberrant hyperproliferation, aberrant dedifferentiation and/or aberrant apoptosis of cells, by ascertaining the level of SIP ligase expression and/or SIP ligase activity in a sample of cells from a patient, and ascertaining the aggressiveness and/or risk for recurrence of the disorder, at enzymatic activity, where an increased level in the sample, relative to a normal control sample of cells, correlates with a more aggressive form of the disorder and an increased risk of recurrence of the disorder.

ACTIVITY - Cytostatic; antipsoriatic; antiarteriosclerotic; antiinflammatory.

MECHANISM OF ACTION - Cell **proliferation**, differentiation, and/or survival modulator; cell-cycle of an eukaryotic cell regulator; entry of a mammalian or yeast cell into S phase modulator; wild-type form of SIP protein agonist/antagonist; gene therapy; antisense therapy. No biological data is given.

USE - (I) is useful for modulating cell **proliferation**, differentiation, and/or survival, and for treating diseases or conditions associated with aberrant protein degradation, cell **proliferation** , differentiation and/or cell survival, where the diseases are selected from cancer, leukemia, psoriasis, bone diseases, **proliferative**

disorders such as involving connective tissues, atherosclerosis, and other **smooth muscle proliferative** disorder, and
chronic inflammation. (I) is useful for mediating and/or catalyzing the transfer of a ubiquitin molecule from a relevant ubiquitin conjugating enzyme (UBC) to a lysine residue of its substrate protein, for regulating the cell-cycle of an eukaryotic cell, for modulating **proliferation** /cell growth of a eukaryotic cell, for modulating entry of a mammalian or yeast cell into S phase, for ubiquitination of a cell-cycle regulator, e.g., a **cyclin dependent kinase** inhibitor,
e.g., **p27**, for modulating differentiation
modulating cell growth or **proliferation** by influencing the action of other cellular proteins, as a specific agonist of the function of the wild-type form of the protein, or as a specific antagonist, such as a catalytically inactive mutant. (I) is useful for generating an interaction trap assay and subsequently detecting agents with disrupt binding of the proteins. A nucleic acid (II) encoding (I) is useful for generating expression constructs and in antisense therapy.
Dwg.0/2

FILE 'REGISTRY' ENTERED AT 15:26:38 ON 24 MAY 2002
E CYCLIN DEPENDENT KINASE INHIBITOR/CN
E CYCLIN DEPENDENT KINASE INHIBITOR P27/CN
L1 5 SEA ABB=ON PLU=ON ("CYCLIN DEPENDENT KINASE INHIBITOR P27"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (HUMAN LGH11 KIDNEY)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (HUMAN P27-KIP1)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (MINK MV1LU CELL N-TERMINAL FRAGMENT)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (MOUSE 1EXLOX EMBRYO)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1 (SUS SCROFA)"/CN OR "CYCLIN DEPENDENT KINASE INHIBITOR P27KIP1R (SUS SCROFA)"/CN)
E "CYCLIN-DEPENDENT KINASE INHIBITOR P27"/CN
L2 1 SEA ABB=ON PLU=ON "CYCLIN-DEPENDENT KINASE INHIBITOR P27KIP1 KINASE"/CN
L3 6 SEA ABB=ON PLU=ON L1 OR L2

FILE 'HCAPLUS' ENTERED AT 15:28:00 ON 24 MAY 2002
L4 458 SEA ABB=ON PLU=ON L3 OR ((CYCLIN DEPENDENT)(2A)KINASE OR CDK)(5A)(P27 OR P 27)

FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:30:26 ON 24 MAY 2002
L5 1460 SEA ABB=ON PLU=ON MARKS A?/AU
L6 1343 SEA ABB=ON PLU=ON MARX S?/AU
L7 105 SEA ABB=ON PLU=ON L5 AND L6
L8 7 SEA ABB=ON PLU=ON L7 AND L4
L9 3 DUP REM L8 (4 DUPLICATES REMOVED)

L9 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001349617 MEDLINE
DOCUMENT NUMBER: 21305844 PubMed ID: 11413088
TITLE: Role for p27(Kip1) in Vascular Smooth Muscle Cell Migration.
COMMENT: Comment in: Circulation. 2001 Jun 19;103(24):2879-81
AUTHOR: Sun J; **Marx S O**; Chen H J; Poon M; **Marks A R**; Rabbani L E
CORPORATE SOURCE: Cardiology Division, Center for Molecular Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: R03-TW-00949 (FIC)
RO1-AI-39794 (NIAID)
RO1-HL-30290 (NHLBI)
RO1-HL-56180 (NHLBI)
SOURCE: CIRCULATION, (2001 Jun 19) 103 (24) 2967-72.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB BACKGROUND: Rapamycin is a potent inhibitor of smooth muscle cell (SMC) proliferation and migration. Rapamycin-mediated inhibition of

SMC proliferation is associated with upregulation of the **cyclin-dependent kinase** inhibitor **p27**(Kip1). Previously, we showed that mixed embryonic fibroblasts obtained from p27(Kip1)(-/-) mice were relatively rapamycin-resistant, suggesting that p27(Kip1) plays an integral role in modulating the antiproliferative effects of rapamycin. We hypothesized that the antimigratory effect of rapamycin may also be mediated by p27(Kip1). METHODS AND RESULTS: Rapamycin (1 to 10 nmol/L) inhibited basic fibroblast growth factor-induced migration of wild-type (WT) but not p27(Kip1)(-/-) SMCs in a dose-dependent manner ($P<0.05$) in a modified Boyden chamber. The effects of rapamycin on aortic SMC explant migration were also studied with WT, p27(+/-), and p27(-/-) mice. Rapamycin 4 mg. kg(-1). d(-1) IP for 5 days inhibited SMC migration by 90% in the WT and p27(Kip1)(+/-) ($P<0.05$) but not p27(Kip1)(-/-) animals. CONCLUSIONS: Lack of p27(Kip1) reduces rapamycin-mediated inhibition of SMC migration. These novel findings suggest a role for p27(Kip1) in the signaling pathway(s) that regulates SMC migration.

L9 ANSWER 2 OF 3 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999233996 MEDLINE
DOCUMENT NUMBER: 99233996 PubMed ID: 10217658
TITLE: Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle.
AUTHOR: Gallo R; Padurean A; Jayaraman T; **Marx S**; Roque M; Adelman S; Chesebro J; Fallon J; Fuster V; **Marks A**; Badimon J J
CORPORATE SOURCE: Cardiovascular Biology Research Laboratory, the Zena and Michael Wiener Cardiovascular Institute, Department of Pathology, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: HL-56180 (NHLBI)
P50-HL-54469 (NHLBI)
RO1-AI-39794 (NIAID)
SOURCE: CIRCULATION, (1999 Apr 27) 99 (16) 2164-70.
Journal code: DAW; 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 20010521
Entered Medline: 19990517

AB BACKGROUND: Although percutaneous transluminal coronary angioplasty (PTCA) is a highly effective procedure to reduce the severity of stenotic coronary atherosclerotic disease, its long-term success is significantly limited by the high rate of restenosis. Several cellular and molecular mechanisms have been implicated in the development of restenosis post-PTCA, including vascular smooth muscle cell (VSMC) activation, migration, and proliferation. Recently, our group demonstrated that rapamycin, an immunosuppressant agent with antiproliferative properties, inhibits both rat and human VSMC proliferation and migration in vitro. In the present study, we investigated (1) whether rapamycin administration could reduce neointimal thickening in a porcine model of restenosis post-PTCA and (2) the mechanism by which rapamycin inhibits VSMCs in

vivo. METHODS AND RESULTS: PTCA was performed on a porcine model at a balloon/vessel ratio of 1.7+/-0.2. Coronary arteries were analyzed for neointimal formation 4 weeks after PTCA. Intramuscular administration of rapamycin started 3 days before PTCA at a dose of 0.5 mg/kg and continued for 14 days at a dose of 0.25 mg/kg. **Cyclin-dependent kinase** inhibitor (CDKI) **p27**(kip1) protein levels and pRb phosphorylation within the vessel wall were determined by immunoblot analysis. PTCA in the control group was associated with the development of significant luminal stenosis 4 weeks after the coronary intervention. Luminal narrowing was a consequence of significant neointimal formation in the injured areas. Rapamycin administration was associated with a significant inhibition in coronary stenosis (63+/-3.4% versus 36+/-4.5%; P<0.001), resulting in a concomitant increase in luminal area (1.74+/-0.1 mm2 versus 3. 3+/-0.4 mm2; P<0.001) after PTCA. Inhibition of proliferation was associated with markedly increased concentrations of the p27(kip1) levels and inhibition of pRb phosphorylation within the vessel wall. CONCLUSIONS: Rapamycin administration significantly reduced the arterial proliferative response after PTCA in the pig by increasing the level of the CDKI p27(kip1) and inhibition of the pRb phosphorylation within the vessel wall. Therefore, pharmacological interventions that elevate CDKI in the vessel wall and target cyclin-dependent kinase activity may have a therapeutic role in the treatment of restenosis after angioplasty in humans.

L9 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 3

ACCESSION NUMBER: 1997:15651 BIOSIS
DOCUMENT NUMBER: PREV199799314854
TITLE: Rapamycin resistance tied to defective regulation of p27-Kip1.
AUTHOR(S): Luo, Yan; **Marx, Steven O.**; Kiyokawa, Hiroaki; Koff, Andrew; Massague, Joan; **Marks, Andrew R. (1)**
CORPORATE SOURCE: (1) Box 1269, Mount Sinai Sch. Med., One Gustave L. Levy Place, New York, NY 10029 USA
SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 12, pp. 6744-6751.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The potent antiproliferative activity of the macrolide antibiotic rapamycin is known to involve binding of the drug to its cytosolic receptor, FKBP12, and subsequent interaction with targets or rapamycin, resulting in inhibition of p70 S6 kinase (p70-S6K). However, the downstream events that lead to inhibition of cell cycle progression remain to be elucidated. The antiproliferative effects of rapamycin are associated with prevention of mitogen-induced downregulation of the **cyclin-dependent kinase** inhibitor **p27**-Kip1, suggesting that the latter may play an important role in the growth pathway targeted by rapamycin. Murine BC3H1 cells, selected for resistance to growth inhibition by rapamycin, exhibited an intact p70-S6K pathway but had abnormally low p27 levels that were no longer responsive to mitogens or rapamycin. Fibroblasts and T lymphocytes from mice with a targeted disruption of the p27-Kip1 gene had impaired growth-inhibitory responses to rapamycin. These results suggest that

the ability to regulate p27-Kip1 levels is important for rapamycin to exert its antiproliferative effects.

=> fil hom
FILE 'HOME' ENTERED AT 15:32:41 ON 24 MAY 2002